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Mortality and Prehospital Blood Pressure in Patients With Major Traumatic Brain Injury
Implications for the Hypotension Threshold

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IMPORTANCE Current prehospital traumatic brain injury guidelines use a systolic blood pressure threshold of less than 90 mm Hg for treating hypotension for individuals 10 years and older based on studies showing higher mortality when blood pressure drops below this level. However, the guidelines also acknowledge the weakness of the supporting evidence.

OBJECTIVE To evaluate whether any statistically supportable threshold between systolic pressure and mortality emerges from the data a priori, without assuming that a cut point exists.

DESIGN, SETTING, AND PARTICIPANTS Observational evaluation of a large prehospital database established as a part of the Excellence in Prehospital Injury Care Traumatic Brain Injury Study. Patients from the preimplementation cohort (January 2007 to March 2014) 10 years and older with moderate or severe traumatic brain injury (Barell Matrix Type 1 classification, *International Classification of Diseases, Ninth Revision* head region severity score of 3 or greater, and/or Abbreviated Injury Scale head-region severity score of 3 or greater) and a prehospital systolic pressure between 40 and 119 mm Hg were included. The generalized additive model and logistic regression were used to determine the association between systolic pressure and probability of death, adjusting for significant/important confounders.

MAIN OUTCOMES AND MEASURES The main outcome measure was in-hospital mortality.

RESULTS Among the 3844 included patients, 2565 (66.7%) were male, and the median (range) age was 35 (10-99) years. The model revealed a monotonically decreasing association between systolic pressure and adjusted probability of death across the entire range (ie, from 40 to 119 mm Hg). Each 10-point increase of systolic pressure was associated with a decrease in the adjusted odds of death of 18.8% (adjusted odds ratio, 0.812; 95% CI, 0.748-0.883). Thus, the adjusted odds of mortality increased as much for a drop from 110 to 100 mm Hg as for a drop from 90 to 80 mm Hg, and so on throughout the range.

CONCLUSIONS AND RELEVANCE We found a linear association between lowest prehospital systolic blood pressure and severity-adjusted probability of mortality across an exceptionally wide range. There is no identifiable threshold or inflection point between 40 and 119 mm Hg. Thus, in patients with traumatic brain injury, the concept that 90 mm Hg represents a unique or important physiological cut point may be wrong. Furthermore, clinically meaningful hypotension may not be as low as current guidelines suggest. Randomized trials evaluating treatment levels significantly above 90 mm Hg are needed.

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The societal burden of traumatic brain injury (TBI) is enormous; each year, TBI leads to 2.2 million emergency department visits, 280 000 hospitalizations, 52 000 deaths, and more than $60 billion in economic costs in the United States.[1,2] In addition, more than 5 million Americans have major long-term disabilities as a result of TBI.[1] Fortunately, there is growing evidence that proper and aggressive management of TBI in the minutes immediately following injury may improve patient outcomes by preventing or lessening secondary brain injury. This has led to the promulgation of evidence-based prehospital and in-hospital TBI treatment guidelines for both children and adults.[3-6]

One major focus of these guidelines is the prevention and treatment of hypotension.[4,5] This is because it has been firmly established that even a single episode of hypotension during the prehospital or early hospital phases of TBI management is associated with dramatic increases in mortality.[3,7-26] Many studies have shown that low blood pressure (variously defined) increases the risk of death. However, the nearly universal assumption that a specific, clinically relevant threshold actually exists is entirely without support. In other words, the design of essentially every relevant study presumes a priori that there is a cut point below which outcome significantly worsens. However, simply dichotomizing small populations and then showing that it is worse to have lower blood pressure than higher blood pressure is not the same as identifying a true threshold. A clinically meaningful cut point would be one that correlates with a marked change in physiological response and patient outcome if blood pressure drops below that particular level. This requires study populations that are large enough to allow evaluation of blood pressure as a continuous variable rather than merely as a categorical variable, eg, low vs not low.

Given the absence of prehospital studies evaluating this specific issue, we analyzed the association between the lowest systolic blood pressure (SBP; obtained prior to hospital arrival) and mortality among children 10 years and older and adults in the Excellence in Prehospital Injury Care (EPIC) TBI Study.[27] Specifically, we tested the null hypothesis that no supportable inflection point in the relationship between SBP and mortality (ie, a threshold) would emerge from the data when evaluated without reference to any given definition for hypotension.

Key Points

Question Is there a prehospital hypotension threshold for mortality in patients with major traumatic brain injury?

Findings In this secondary analysis of the Excellence in Prehospital Injury Care Traumatic Brain Injury Study, the association between systolic blood pressure and adjusted probability of death was monotonic across a broad range (40-119 mm Hg), with each 10-point increase in systolic pressure associated with a decrease of 18.8% in the adjusted odds of death.

Meaning In patients with traumatic brain injury, the concept that 90 mm Hg represents a unique or important physiological cut point may be wrong, and clinically meaningful hypotension may not be as low as current guidelines suggest.

Methods

Study Design, Setting, and Oversight

The parent study, EPIC, is evaluating the effect of implementing the prehospital TBI guidelines[3-6] for patients with major (ie, moderate or severe) TBI throughout Arizona. This is being done by using a before-after, multisystem, observational design. The study is expected to be completed in 2017 and has been described in detail elsewhere.[27] Rather than reiterating the details of the parent study here, we limit the description to the design attributes relevant to this specific secondary analysis. The patients in this evaluation are in the preimplementation cohort of the EPIC TBI Study. Postinterventional patients were excluded, since one of the emphases of guideline implementation is the prevention and aggressive treatment of hypotension. Thus, including these patients might introduce significant bias into this evaluation, as there was no intentional guideline implementation prior to the EPIC TBI Study.

The necessary regulatory approvals for the EPIC TBI Study have been obtained from the Arizona Department of Health Services and the State Attorney General. The University of Arizona Institutional Review Board and the Arizona Department of Health Services Human Subjects Review Board have approved the project and have determined that, by virtue of being a public health initiative, neither the interventions nor their evaluation constitute human subjects research and have waived informed consent and approved the publication of deidentified data.

Data Collection

The Arizona State Trauma Registry contains extensive trauma center data on all patients taken to the 8 designated level I trauma centers in the state. From the Arizona State Trauma Registry, all patients meeting study criteria were entered into the EPIC database. Each participating emergency medical services (EMS) agency then received a list of the patients in the EPIC TBI Study that were cared for in their system. The patients were matched by incident date, name, and other patient identifiers. Either scanned copies (paper-based patient care records [PCRs]) or electronic data files (electronic PCRs) were then sent to the study data center for entry into the EPIC database. This provided an extensive linked data set for study patients, which includes both prehospital and trauma center data. The entire process of identifying patients, linking EMS and trauma center data, accessing EMS PCRs, entering data, and structuring the EPIC database have been reported.[27] More than 20 000 patients have been enrolled in the EPIC TBI Study and more than 31 000 EMS PCRs have been entered into the database (patients cared for by multiple agencies have more than 1 PCR). The successful linkage rate is exceptionally high (eg, throughout the study, patients with missing data for SBP has been consistently less than 5%).

Participants

Inclusion criteria for the EPIC Study were physical trauma, a trauma center diagnosis(es) consistent with TBI (ie, either

isolated or multisystem trauma that includes TBI), and at least one of the following definitions for moderate or severe TBI: Barell Matrix Type 1 classification, *International Classification of Diseases, Ninth Revision* head region severity score of 3 or greater, and/or Abbreviated Injury Scale head-region severity score of 3 or greater.[27]

Exclusion criteria for this subgroup analysis included age younger than 10 years, an SBP less than 40 mm Hg or 120 mm Hg or greater, interhospital transfers, and death before arrival to the emergency department. In addition, patients that were missing data for age, SBP, or trauma type (ie, penetrating vs blunt) were excluded. The 120 mm Hg upper limit was chosen because this represents the highest reported threshold in the previous literature[7-9,11,14,15,17-22,26,28-36] and because including a large number of patients with near-normal or normal perfusion in the mortality model would dilute the effects of the patients who are actually at risk for hypoperfusion.

Interventions

This is a secondary analysis of the preimplementation cohort and entails no interventions.

Main Outcome

The outcome is in-hospital mortality.[27]

Statistical Analysis

Continuous variables were summarized by median and range and were compared between the 2 cohorts (survived vs died) using the Wilcoxon rank sum test. Categorical variables were summarized by frequency and proportion (with 95% CIs) when appropriate and were compared between the 2 groups by Fisher exact test.

The overall trend in crude (unadjusted) mortality rates over the range of lowest prehospital SBP was explored using moving average plots. To plot the moving average, the crude death rate and corresponding 95% CI were calculated for patients with lowest SBP in each interval spanning 10 consecutive values (ie, 40-49 mm Hg, 41-50 mm Hg, 42-51 mm Hg, and so on, through 110-119 mm Hg). The estimated death rate and corresponding 95% CI were plotted against the midpoint of the interval (ie, the range of plotting is 44.5 mm Hg for 40-49 mm Hg, and so on, through 114.5 for the 110-119 mm Hg interval). The moving window of 10 mm Hg was selected to prevent any false cut points being created by data anomalies in the frequency of the last digit of lowest recorded SBP (eg, in the data set, even numbers were preferred to odd numbers, and the digit 0 was the most popular, followed by 8 and 6). Thus, using a window length of 10 prevents abnormalities arising from the uneven recording distribution of the last SBP digit.

The risk-adjusted associations between mortality and SBP were examined by logistic regression, which modeled the log odds of death, adjusting for important risk factors and potential confounders (ie, age, sex, race/ethnicity, payment source, trauma type, prehospital hypoxia, prehospital intubation, and treating trauma center). The linkage of EMS data to the Arizona State Trauma Registry allowed the use of actual diagnostic/anatomic injury scoring to adjust for overall injury severity (Injury Severity Score)[37] and TBI severity (*International Classification of Diseases, Ninth Revision* head injury diagnoses matched to Abbreviated Injury Scale head-region score)[38-44] rather than having to rely on far less reliable prehospital physiological injury indicators (eg, Glasgow Coma Scale score). The effects of continuous variables (ie, SBP and age) in the logistic regression were fitted nonparametrically using penalized thin plate regression splines through the generalized additive model.[45] The model was penalized to avoid overfitting (excessive "wiggliness" in the transformation function due to random noise), and the smoothing parameters were chosen to optimize the Akaike Information Criterion, a measure of the predictive power of the model.[45] Thus, the functional forms of these variables were determined by the data.

The software environment R was used for the analysis,[46] and the R package mgcv[45,47] was used for the generalized additive model. *P* values were calculated from a Wald-type test using the Bayesian covariance matrix.[48] All tests were 2-sided with $\alpha = .05$.

Results

Enrollment

There were 17 105 patients in the preintervention group from January 2007 to March 2014. Excluded were 1162 children (6.8%) younger than 10 years, 4823 (28.2%) interfacility transfers, and 6352 (37.1%) with a lowest prehospital SBP less than 40 mm Hg or 120 mm Hg or greater as well as 924 (5.4%) with missing data (SBP, 300; transfer status, 623; and trauma type, 1). This left 3844 patients (22.5%) in our study cohort.

Outcome and Analysis

Among these 3844 patients, 528 (13.7%) died. **Table 1** summarizes the demographic information and patient characteristics by survival status. **Figure 1** shows the crude (unadjusted) moving average of death rate by lowest EMS SBP. This plot reveals a relatively steady slope from 40 mm Hg to nearly 110 mm Hg. A logistic regression model was fitted that examined the effect of lowest prehospital SBP on mortality risk, controlling for risk adjusters and potential confounders. For continuous variables (ie, SBP and age), the functional form of the covariate effect was obtained nonparametrically with the value of the smoothing parameter calculated to optimize the Akaike Information Criterion. All other confounders were categorical (Table 1). **Table 2** shows the effects and *P* values of all covariates in the model (except for the continuous variables and treating trauma center, which were all significant at $P < .001$). As has been found by many previous studies,[7,8,11,17,18,49,50] hypoxia was a highly significant risk factor and was included as a confounder in the model. The data by trauma center, while parametric, are not shown in **Figure 2**. Because absolute anonymity is required by state regulations and the institutional review board (for patients, EMS agencies, and hospitals), we are not able to report specific trauma center-related data, even generically; because trauma center volumes are a matter of public record, presentation of these data could conceivably lead to hospital-specific information being inferred or identified (eg, because of comparisons of the sizes of the 95% CIs). However,

Table 1. Patient Characteristics by Survival Status

Characteristic[a]	No. (%) Alive (n = 3316)	No. (%) Dead (n = 528)	*P* Value[b]
Age, median (range), y	34 (10-99)	42 (10-95)	<.001
Male			
No	1125 (33.9)	154 (29.2)	.04
Yes	2191 (66.1)	374 (70.8)	
Race			
African American	101 (3)	15 (2.8)	
Asian	38 (1.1)	5 (0.9)	
American Indian/Alaska Native	239 (7.2)	27 (5.1)	.53
White	2548 (76.8)	405 (76.7)	
Other	360 (10.9)	61 (11.6)	
Unknown	30 (0.9)	15 (2.8)	
Hispanic ethnicity			
No	2443 (73.7)	376 (71.2)	>.99
Yes	785 (23.7)	120 (22.7)	
Unknown	88 (2.7)	32 (6.1)	
Payer			
Private insurance	1291 (38.9)	139 (26.3)	
AHCCCS/Medicaid	987 (29.8)	136 (25.8)	
Medicare	356 (10.7)	85 (16.1)	<.001
Self-pay	497 (15)	115 (21.8)	
Other	151 (4.6)	25 (4.7)	
Unknown	34 (1)	28 (5.3)	
Trauma type			
Blunt	3196 (96.4)	392 (74.2)	<.001
Penetrating	120 (3.6)	136 (25.8)	
ICD-9 head region severity score			
1-3	2060 (62.1)	40 (7.6)	
4	883 (26.6)	53 (10)	<.001
5-6	331 (10)	425 (80.5)	
Unknown	42 (1.3)	10 (1.9)	
ICD-9 injury severity score			
1-14	1317 (39.7)	5 (0.9)	
16-24	1038 (31.3)	19 (3.6)	<.001
≥25	961 (29)	504 (95.5)	
Prehospital minimum SBP, median (range), mm Hg	107 (40-119)	92 (40-119)	<.001
Prehospital hypoxia			
No	2886 (87)	274 (51.9)	
Yes	282 (8.5)	162 (30.7)	<.001
Unknown	148 (4.5)	92 (17.4)	
Prehospital intubation			
No	2863 (86.3)	202 (38.3)	<.001
Yes	453 (13.7)	326 (61.7)	

Abbreviations: AHCCS, Arizona Health Care Cost Containment System; *ICD-9*, *International Classification of Diseases, Ninth Revision*; SBP, systolic blood pressure.

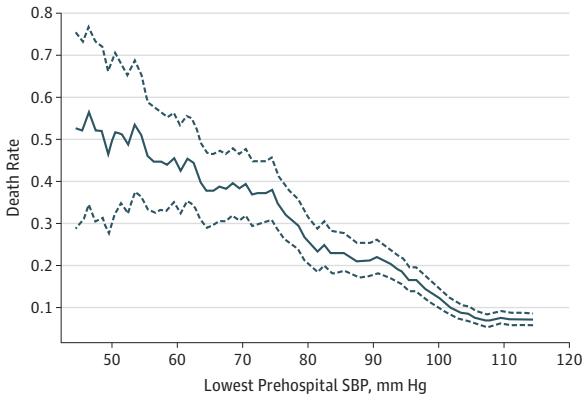
[a] Trauma center was also highly significant (not shown; $P < .001$).

[b] Fisher exact test used for categorical variables and Wilcoxon rank sum test used for continuous variables.

because treating trauma center was a significant confounder, we adjusted for it in the model.

In the optimal model (based on Akaike Information Criterion), the adjusted effect of lowest SBP on log odds of death was nearly perfectly linear, with an adjusted odds ratio of 0.812 (95% CI, 0.748-0.883; $P < .001$) associated with a 10-mm Hg increase in SBP at any level between 40 and 120 mm Hg (eg, a patient with an SBP of 110 mm Hg has an 18.8% lower adjusted odds of death than one with an SBP of 100 mm Hg, and so on throughout the entire range). Figure 2 shows the adjusted probability of death over the range of 40 to 120 mm Hg. As can be seen, the rate of change in estimated probability of

Figure 1. Unadjusted Moving Average of Death Rate by Lowest Systolic Blood Pressure (SBP)



The solid line represents the moving average of the estimated death rate for each interval spanning 10 consecutive values, and the dotted lines represent the pointwise 95% CIs.

death is essentially constant. In other words, there is a striking absence of any identifiable threshold of SBP in relationship to mortality, and major reductions in both crude and adjusted mortality continue far to the right of the classic 90 mm Hg hypotension level. Additional evidence comes from the receiver operating characteristic curve plot of the data. The area under the curve is 0.705, and there is no cut point that gives satisfactory levels of both sensitivity and specificity to indicate a threshold.

Discussion

The previous literature related to this investigation consists of studies that were small,[7,8,11,14-21,23,24,26,29,30,34,50] had limited or no prehospital data,[7,11,14-17,20,21,24,26,28,29,34,36,50] or evaluated general trauma populations (ie, were not specific to patients with TBI).[35,51-55] The current study is unique in both its size and its access to detailed prehospital data. A key reason for evaluating the effect of blood pressure measured before hospital arrival is because the injured brain is so highly sensitive to changes in perfusion, and the timeframe during which neuronal damage begins is so short. It is well established that secondary brain injury is initiated by even brief periods of compromised blood flow.[4,5,11-13,17,20,27] Thus, decreased perfusion occurring during the prehospital time interval may have a profound effect on outcome. Indeed, our results reveal a strong, independent association between mortality and blood pressure measured in the field. This is remarkable, given the large number of factors that potentially affect survival in patients with TBI. It appears that the effectiveness of subsequent interventions may be highly dependent on patients who are neurologically viable being delivered to the trauma center so they have the potential to benefit from subsequent specialized care.

One of the most striking aspects of the literature evaluating the association between blood pressure and TBI mortality is the underlying assumption that there is a clinically relevant threshold. Some might argue that this is merely an operational reality inherent to the studies, that some level of

Table 2. Parametric Terms in the Multivariate Logistic Regression Model for Death

Covariate[a]	Odds Ratio (95% CI)[b]	*P* Value
Male		
No	1 [Reference]	.54
Yes	0.91 (0.67-1.23)	
Race		
African American	1 [Reference]	
Asian	1.09 (0.22-5.37)	
American Indian/Alaska Native	1.02 (0.36-2.88)	.75
White	1.29 (0.53-3.11)	
Other	1.19 (0.42-3.36)	
Unknown	2.89 (0.66-12.75)	
Hispanic ethnicity		
No	1 [Reference]	.06
Yes	0.61 (0.40-0.92)	
Unknown	1.03 (0.46-2.34)	
Payer		
Private	1 [Reference]	
AHCCCS/Medicaid	1.24 (0.86-1.78)	
Medicare	1.72 (1.00-2.97)	<.001
Self-pay	3.65 (2.36-5.65)	
Other	1.76 (0.89-3.48)	
Unknown	9.56 (3.78-24.16)	
Trauma type		
Blunt	1 [Reference]	<.001
Penetrating	3.89 (2.53-5.98)	
ICD-9 head region severity score		
1-3	1 [Reference]	
4	1.34 (0.82-2.20)	<.001
5-6	13.2 (8.41-20.72)	
Unknown	6.31 (2.36-16.86)	
ICD-9 injury severity score		
1-14	1 [Reference]	<.001
16-24	2.63 (0.91-7.60)	
≥25	15.96 (6.00-42.50)	
Prehospital hypoxia		
No	1 [Reference]	<.001
Yes	1.89 (1.35-2.65)	
Unknown	4.3 (2.71-6.83)	
Prehospital intubation		
No	1 [Reference]	<.001
Yes	2.81 (2.08-3.78)	

Abbreviations: AHCCS, Arizona Health Care Cost Containment System; *ICD-9*, *International Classification of Diseases, Ninth Revision*; SBP, systolic blood pressure.

[a] Also adjusted for trauma centers (not shown; $P < .001$).

[b] Odds ratio for death compared with the referent category.

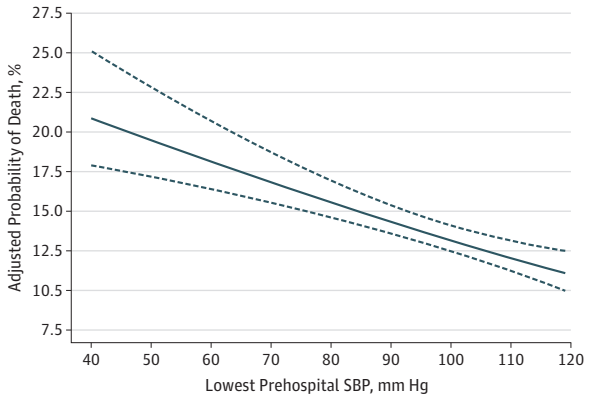
hypotension must be chosen as a treatment threshold. However, even if the threshold concept isn't always explicitly affirmed, its use is so ubiquitous that, functionally, it is treated as a given in the literature. In other words, there is a nearly universal concept of the existence of a level of SBP that represents a cut point, below which it is highly deleterious to drop.

However, the results of the current investigation seem to provide a significant contrast to current thinking about the implications of hypotension in the early care of patients with TBI. Visually evaluating the plot of adjusted mortality risk vs SBP (Figure 2) reveals a surprising finding—the absence of even a hint of a cut point at any level between 40 and 120 mm Hg. In addition, the mathematical expression of the data verifies this visual impression in that the association between SBP and the adjusted log odds of death is linear, with an adjusted odds ratio of 0.812 for mortality associated with a 10-mm Hg increase, regardless of the level being assessed. Thus, any 2 patients with an SBP difference of 10 mm Hg differ in their adjusted odds of death by 18.8%, which holds true across the entire SBP range. These results raise the possibility that, perhaps, no threshold exists in the sense that the concept is typically used. It appears that the threshold concept may have been artificially generated by investigations that, because of their small size, basically had no alternative but to deal with prehospital blood pressure dichotomously (ie, comparing low with not low). However, as this literature grew, the concept gained momentum and was incorporated into guidelines.

Another notable finding revealed by Figure 2 is the lack of a change in the slope even as the plot moves far to the right of the commonly applied definition for hypotension. This raises the possibility that clinically meaningful hypotension may not be as low as is currently thought for the injured brain. Indeed, despite the specifically recommended threshold, guidelines from the Brain Trauma Foundation also state that it is unclear what the threshold ought to be. Hence the explicit statement in the section on resuscitation end points: "The value of 90 mm Hg as a threshold for hypotension has been defined by blood pressure distributions for *normal* adults [emphasis added]. Thus, this is more a statistical than physiological finding."[5] Furthermore, the document goes on to forthrightly admit ambivalence about the recommended threshold: "Given the influence of cerebral perfusion pressure on outcome, it is possible that SBP higher than 90 mm Hg would be desirable during the prehospital and resuscitation phase, but no studies have been performed to corroborate this."[5] The lack of clarity surrounding this issue led the guideline authors to give it high priority in the section on "Key Issues for Future Investigation." In the listing of recommended future research, the first topic is the identification of "the level of hypotension that correlates with poor outcome."[5]

A careful reading of the extant studies reflects the complexity of defining hypotension in the setting of TBI. In fact, the literature varies widely and contains reports that have used cut points as low as 79 mm Hg and as high as 120 mm Hg in adults.[7-9,11,14,15,17-22,26,28-36] Furthermore, the size and design of these studies preclude them from identifying "the" threshold, even if one actually exists. If previous prehospital studies had been larger, they would have been able to identify significant differences in outcomes using a wide range of potential thresholds, thereby revealing the arbitrary nature of choosing any one particular level.

Figure 2. Adjusted Probability of Death by Lowest Systolic Blood Pressure (SBP)



Adjusted probability of death shown over the range of 40 to 120 mm Hg. The rate shown is the marginal rate, in the sense that at any fixed value of SBP, the rate is the average of the predicted death rates for all patients in the data set with the SBP value changed to the fixed value and with values of all other covariates unchanged from the actual observed values. The dotted lines represent the pointwise 95% CIs.

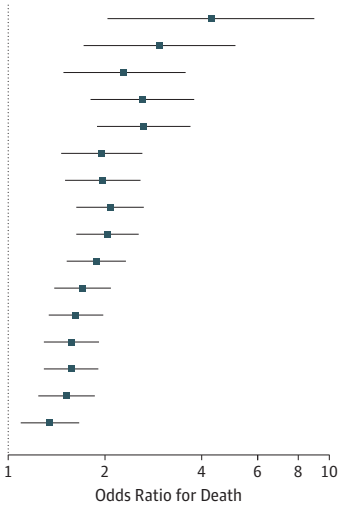
To highlight this limitation in the current literature, we analyzed a broader cohort of patients in the EPIC database (SBP, 40-200 mm Hg) and dichotomized the cohort as "low" vs "not low" using various cut points in increments of 5 mm Hg. This yields the remarkable result that there is a statistically significant difference in the adjusted probability of death for thresholds as low as 60 mm Hg and as high as 135 mm Hg (**Figure 3**). In other words, one can pick any cut point throughout this range and obtain significant findings. Despite decades of assuming otherwise, it appears that the interaction between prehospital blood pressure and outcome may be physiologically continuous rather than dichotomous across a remarkably wide range. While it is hard to conceive of an approach to managing TBI that doesn't include some level of blood pressure that requires treatment, it appears that the science that forms the basis for the current guidelines may require an entirely new way of thinking.

Limitations

This study has limitations. First, the design is observational. Thus, we cannot establish cause and effect relationships associated with the treatment of hypotension. For instance, these data do not prove that the therapeutic target for blood pressure should be higher than the current recommendations. However, they do highlight the great importance of perfusing the injured brain and that blood pressure is powerfully linked to outcome.[16,25,28] Furthermore, these results do

Figure 3. Wide-Ranged Systolic Blood Pressure (SBP) Thresholds and Adjusted Odds Ratios of Death

Threshold, mm Hg	Odds Ratio (95% CI)
<60 vs ≥60	4.3 (2.1-8.9)
<65 vs ≥65	3.0 (1.7-5.1)
<70 vs ≥70	2.3 (1.5-3.6)
<75 vs ≥75	2.6 (1.8-3.8)
<80 vs ≥80	2.6 (1.9-3.7)
<85 vs ≥85	2.0 (1.5-2.6)
<90 vs ≥90	2.0 (1.5-2.6)
<95 vs ≥95	2.1 (1.6-2.6)
<100 vs ≥100	2.0 (1.6-2.5)
<105 vs ≥105	1.9 (1.5-2.3)
<110 vs ≥110	1.7 (1.4-2.1)
<115 vs ≥115	1.6 (1.3-2.0)
<120 vs ≥120	1.6 (1.3-1.9)
<125 vs ≥125	1.6 (1.3-1.9)
<130 vs ≥130	1.5 (1.2-1.9)
<135 vs ≥135	1.3 (1.1-1.7)



The cohort of patients from the Excellence in Prehospital Injury Care study whose lowest prehospital SBP was between 40 and 200 mm Hg was dichotomized into "low" vs "not low" groups using various cut points in increments of 5 mm Hg. Logistic regression was used to estimate the odds ratio of death between the 2 groups, adjusting for factors shown in Table 2. Squares indicate estimated adjusted odds ratios, and error bars indicate 95% CIs.

appear to support the statements in the TBI guidelines cautioning that the current recommendations may allow blood pressure to drop too low before intervening. A related concern is that we have not accounted for treatment of hypotension in the model. The parent study is designed specifically to identify the influence of treatment on outcomes using a controlled before-after system design, and the Analysis Plan[27] includes only an interim analysis (completed) and a final analysis (scheduled) and does not allow for multiple looks at the interventional data. Thus, to prevent any encroachment on the main study hypotheses, we are deferring all evaluations of treatment effects until the final analysis. Second, this evaluation does not inform questions associated with blood pressure management after the early resuscitative phase of care. This is true for several reasons; ongoing pressure monitoring in neurocritical care uses mean arterial pressure and cerebral perfusion pressure rather than SBP, and the prehospital management of blood pressure focuses solely on treating hypotension.[4] Thus, the implications of our study cannot be used to inform issues associated with ongoing intensive care unit management or controversies, such as enhancing/optimizing perfusion.[56,57] Third, there were some missing data. However, for a prehospital study, the rate of missing data is extremely low (eg, 1.8% missing data for SBP; no missing data for mortality). Fourth, the database contains only those SBPs that were documented by EMS. Thus, we cannot know for sure that the reported measurements reflected the actual lowest SBP. Finally, there is no way to independently verify the accuracy of blood pressure measurements. However, this is true of essentially all EMS investigations.[58] One great advantage of the EPIC TBI Study is that the data team abstracts the PCRs directly and comprehensively. This level of scrutiny and consistency of data access is rare in prehospital research.[58]

Conclusions

In a statewide, multisystem analysis of patients with major TBI, we found a linear association between the lowest prehospital SBP and the severity-adjusted probability of death across an exceptionally wide range. This suggests that there may not be a clinically meaningful threshold. Furthermore, for the injured brain, physiologically detrimental hypotension may occur at significantly higher levels than current guidelines suggest. These findings highlight the need for specific trials comparing various blood pressure treatment thresholds well above the classic 90 mm Hg.

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Body Temperature after EMS Transport: Association with Traumatic Brain Injury Outcomes

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Body Temperature after EMS Transport: Association with Traumatic Brain Injury Outcomes

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Abstract

Introduction: Low body temperatures following prehospital transport are associated with poor outcomes in patients with traumatic brain injury (TBI). However, a minimal amount is known about potential associations across a range of temperatures obtained immediately after prehospital transport. Furthermore, a minimal amount is known about the influence of body temperature on non-mortality outcomes. The purpose of this study was to assess the correlation between temperatures obtained immediately following prehospital transport and TBI outcomes across the entire range of temperatures. **Methods**: This retrospective observational study included all moderate/severe TBI cases (CDC Barell Matrix Type 1) in the pre-implementation cohort of the Excellence in Prehospital Injury Care (EPIC) TBI Study (NIH/NINDS: 1R01NS071049). Cases were compared across four cohorts of initial trauma center temperature (ITCT): <35.0°C [Very Low Temperature (VLT)]; 35.0–35.9°C [Low Temperature (LT)]; 36.0–37.9°C [Normal Temperature (NT)]; and ≥38.0°C [Elevated Temperature (ET)]. Multivariable analysis was performed adjusting for injury severity score, age, sex, race, ethnicity, blunt/penetrating trauma, and payment source. Adjusted odds ratios (aORs) with 95% confidence intervals (CI) for mortality were calculated. To evaluate non-mortality outcomes, deaths were excluded and the adjusted median increase in hospital length of stay (LOS), ICU LOS and total hospital charges were calculated for each ITCT group and compared to the NT group. **Results**: 22,925 cases were identified and cases with interfacility transfer (7361, 32%), no EMS transport (1213, 5%), missing ITCT (2083, 9%), or missing demographic data (391, 2%) were excluded. Within this study cohort the aORs for death (compared to the NT group) were 2.41 (CI: 1.83–3.17) for VLT, 1.62 (CI: 1.37–1.93) for LT, and 1.86 (CI: 1.52–3.00) for ET. Similarly, trauma center (TC) LOS, ICU LOS, and total TC charges increased in all temperature groups when compared to NT. **Conclusion**: In this large, statewide study of major TBI, both ETs and LTs immediately following prehospital transport were independently associated with higher mortality and with increased TC LOS, ICU LOS, and total TC charges. Further study is needed to identify the causes of abnormal body temperature during the prehospital interval and if in-field measures to prevent temperature variations might improve outcomes. **Key words:** hyperthermia; traumatic brain injury; hypothermia; mortality; cost

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Introduction

In 2010, Traumatic Brain Injury (TBI) led to over 1.7 million emergency department visits, 275,000 hospitalizations, and 50,000 deaths in the United States.[1,2] The lifetime cost of TBI sustained in the year 2000 alone was estimated to be over 60 billion US dollars[3,4] with more than 2% of the US population requiring long-term assistance as a result of TBI.[5] Secondary brain injury is a major contributor to increased morbidity and mortality following TBI. Several factors have been identified as causing secondary brain injury during prehospital care including: hypotension, hypoxia, and hyperventilation.[6–17] Through multiple pathophysiological mechanisms, both elevated body temperature and low body temperature could cause secondary brain injury with resulting increases in morbidity and mortality.[18–23]

Low body temperatures in the prehospital setting have long been known to be associated with poor outcomes in general trauma patients. In this population, multiple studies have reported that body temperature <35°C is associated with a marked increase in the adjusted odds of death when compared to

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patients with normal body temperature.[20,22,24–26] However, the vast majority of available data on hypothermia in TBI has focused on therapeutic hypothermia as a modality to improve outcomes in the intensive care unit (ICU).[27–29]

Even less is known about the effect of elevated temperatures on TBI outcomes.[18,21,23] Patients with severe TBI are known to frequently develop idiopathic elevated temperatures ("neurogenic fever") during their hospital course. These elevated temperatures have been associated with poor outcomes and increased mortality.[30–35] Although poorly understood, it is thought that temperature abnormalities in the ICU are a result of Central Nervous System (CNS) failure to regulate temperature following injury.[36] However, these mechanisms that lead to fluctuations in body temperature during the hospital course may not be the primary cause of elevated temperatures identified on initial presentation to the ED.[19] This is more likely due to environmental exposure that occurs from the time of injury until the patient arrives at the hospital. However, a minimal amount is known about the incidence and outcomes of TBI patients who already have elevated body temperature by the end of their prehospital interval.

The purpose of the current study is to evaluate potential associations between body temperature immediately following prehospital transport and various outcomes in victims of major TBI.

METHODS

Study Design

This study is a retrospective observational analysis of data contained in the Arizona State Trauma Registry (ASTR) and the Excellence in Prehospital Injury Care (EPIC) TBI database. The ASTR database contains information on all trauma patients cared for at level 1 trauma centers (TCs) in Arizona (total of 8 TCs) and was matched with prehospital data for participating EMS agencies transporting patients to one of the TCs. More than 90% of TBI patients in Arizona were cared for by agencies participating in the EPIC project. The details of the EPIC Study, a statewide, before/after, controlled evaluation of the impact of implementing the EMS TBI treatment guidelines (NIH/NINDS: 1R01NS071049; ClinicalTrials.gov: #NCT01339702), have been reported in detail elsewhere.[37]

Data Validity Efforts

The ASTR data validation tool, developed collaboratively by Arizona Department of Health Services (ADHS) staff and the trauma registry software vendor significantly increases the ASTR data quality. More than 800 data checks are performed per record for the full data set. Data checks include warning flags for blank fields, invalid entries, date and time errors, and other data logic errors. The Data and Quality Assurance (DQA) staff within ADHS run validation reports and the results are sent to the reporting hospitals so that the data can be updated, confirmed, and resubmitted to the ASTR with changes. The DQA section also performs statewide inter-rater reliability testing as a quality assurance tool to continuously improve on trauma data entry standardization and data reliability.

Study Population and Setting

Cases of moderate/severe ("major") TBI in the State of Arizona, occurring between January 1, 2007 and December 31, 2012 were identified using the ASTR/EPIC database. In the EPIC Study, major TBI is defined as those patients with physical trauma who have trauma center diagnosis(es) consistent with TBI (either isolated or multisystem trauma that includes TBI) and meet at least one of the following definitions for moderate or severe TBI: a) Centers for Disease Control (CDC) Barell Matrix-Type 1; b) Head Region Severity Score (International Classification of Diseases-ICD-9) ≥ 3; and/or c) Abbreviated Injury Scale (AIS)-Head Region Severity Score ≥ 3.[37] Cases were excluded if temperature on arrival to the TC was not recorded, temperature was recorded after a transfer from a non-TC to a TC, or if other important risk adjusters were missing. The included patients were cared for by more than 100 different EMS agencies. We are not aware of any attempt to specifically detect, prevent, or treat temperature abnormalities in the prehospital setting.

Human Subjects Review

The necessary regulatory approvals for EPIC have been obtained from the Arizona Department of Health Services (ADHS) and the State Attorney General. The University of Arizona Institutional Review Board and the ADHS Human Subjects Review Board have approved the project and publication of de-identified data.[37]

Statistical Analysis

All cases of major TBI in the EPIC/ASTR data set were evaluated. Those with an interfacility transfer and those without a documented ITCT or missing important risk adjusters (e.g., race, ISS, payment source) were excluded. The unadjusted association between the continuous variable ITCT and mortality was first evaluated using a Lowess smoothing function, with the outcome transformed to logits (log odds), in order to assess whether body temperature was linearly related to the outcome in the logit, a key requirement for continuous variables in logistic regression. Fractional polynomial

regression was used to find a transformation for ITCT as a continuous variable for logistic regression to satisfy the requirement of linearity in the logit. ITCT was also categorized using the following four commonly-used clinical cutoffs for abnormal body temperatures: very low temperatures (<35.0°C), low temperatures (35.0–35.9°C), normal temperatures (36.0–37.9°C), and elevated temperatures (≥38.0°C). Non-mortality outcomes were evaluated utilizing the sub-group of patients who survived. A severity-adjusted analysis (outlined in the following section) was then used to compare mortality and non-morality outcomes among the four temperature-defined groups.

Measurements and Key Outcomes

The outcomes for this study were in-hospital mortality following the initial injury and other commonly reported non-mortality outcomes: TC length-of-stay, intensive care unit (ICU) length of stay, and total TC charges in US Dollars ($).

Analysis

A multivariable risk adjustment analysis was performed comparing mortality between the very low temperature, low temperature, and elevated temperature groups to that of the cases with normal temperature. The covariates for the severity adjusted analysis were chosen a priori, based on the known or suspected relationship (either directly or as a potential confounder) to the main outcome variable, mortality, and accounted for: injury severity scale (ISS), age, sex, race, ethnicity, trauma type (blunt vs. penetrating), and payment source (private, public, self, other) as describe elsewhere.[37] The results of the logistic regression model are reported as adjusted odds ratios (aOR) with 95% Confidence Intervals (CI) for mortality among each group when compared to those in the NT group. Median regression was used to model the severity adjusted median difference in non-mortality outcomes between the very low temperature, low temperature, and elevated temperature groups to those cases with normal temperature after adjusting for ISS, age, sex, and trauma type. Statistical analyses were conducted using SAS v9.3 (SAS Institute, Inc., Cary, NC) and Stata v14 (StataCorp LP, College Station, TX).

RESULTS

The EPIC TBI database contained 22,925 cases of major TBI, out of which 11,877 (51.8%) were included in the study. Of the 22,925 cases identified 2,083 (9.1%) were excluded due to missing ITCT data. An additional 7,361 (32.1%) cases were excluded because they were interfacility transfers and 1213 (5.3%) due to transport by private vehicle. An additional 391 (1.7%) cases were excluded either due to missing information on race, ISS, or payment source leaving 11,877 cases included in this study. The demographic data for the study population stratified by ITCT group are shown in Table 1. Most cases (70.1%) were men and median age was 39 years. The majority (58.6%) had an ISS >15 and had a blunt mechanism of injury (95.6%). Patients excluded due to missing ITCT were more likely to be seriously injured (79.9% with an ISS > 15) and less likely to have blunt injury (85.6%).

Figure 1 shows the plot of ITCT versus the unadjusted log odds (logit) of death using a Lowess smoothing function, which suggests a non-linear relationship between ITCT and the outcome in the logit scale. Fractional polynomial regression failed to find an adequate transformation of the continuous variable that was linearly associated with the log odds of death, a key requirement of logistic regression. Thus, ITCT categorized into 4 categories, based on commonly used clinical definitions of body temperature abnormalities, was used for all analyses.

TABLE 1. Study population demographic data

	Initial Trauma Center Temperature				
	<35°C	35–35.9°C	36–37.9°C	≥38°C	Total TBI
Total Patients	473 (4.0%)	2,256 (19.0%)	8,971 (75.5%)	177 (1.5%)	11,877
Male	350 (73.9%)	1,581 (70.0%)	6,266 (69.8%)	134 (75.7%)	8,331 (70.1%)
Age in Years (Q1-Q3)	36 (22–54)	39 (22–58)	39 (22–57)	37 (20–55)	39 (22–57)
Race					
Hispanic	74 (15.6%)	532 (23.5%)	2,189 (24.4%)	48 (27.1%)	2,843 (23.9%)
White	305 (64.4%)	1419 (62.8%)	5,555 (61.9%)	101 (57.0%)	7,380 (62.1%)
Other	94 (19.8%)	305 (13.5%)	1,227 (13.6%)	28 (15.8%)	1,654 (13.9%)
Injury Severity Score (ISS) > 15	407 (86.0%)	1,655 (73.3%)	4,763 (53.0%)	136 (76.8%)	6,961 (58.6%)
Payer					
Public Insurance	219 (46.3.%)	1,095 (48.5%)	4,092 (45.6%)	79 (44.6%)	5,485 (46.2%)
Private Insurance	162 (34.2%)	786 (34.8%)	3,294 (36.7%)	65 (36.7%)	4,307 (%36.3)
Other Insurance	92 (19.4%)	375 (16.6%)	1,585 (17.6%)	33 (18.6%)	2,085 (17.6%)
Blunt Trauma	423 (89.4%)	2,110 (93.5%)	8,658 (96.5%)	167 (94.3%)	1,1358 (95.6%)
Mortality	147 (31.0%)	365 (16.1%)	565 (6.2%)	32 (18.0%)	1,109 (9.3%)

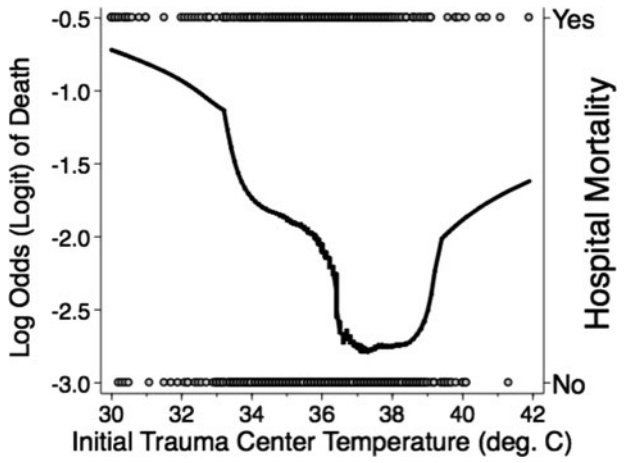

FIGURE 1. Lowess smoothing function for unadjusted mortality versus initial trauma center temperature.

TABLE 3. Non-mortality adjusted median regression analysis

Temperature	Median Hospital LOS (95% CI)	Median ICU LOS (95% CI)	Median Hospital Charges (95% CI)
≥ 38°C	2.38 (1.94–2.81)	1.29 (1.18–1.40)	$42,714 (36,853–48,574)
36–37.9°C	Referent	Referent	Referent
35–35.9°C	1.07 (0.94–1.21)	0.41 (0.38–0.45)	$11,599 (9,846–13,352)
< 35°C	2.84 (2.52–3.13)	1.29 (1.22–1.37)	$37,135 (33,214–41,055)

Values reported represent the adjusted increase in LOS or hospital charges with (95% Confidence Intervals) in each group when compared to the median value for the 36–37.9°C group.

The normal temperature group accounted for 75.5% (n = 8,971) of the total study population, while there were 2,256 (19.0%) in the low temperature group, 473 (4.0%) in very low temperature group, and 177 (1.5%) in the elevated temperature group. Injury severity scores were higher in the elevated temperature, low temperature and very low temperature groups than in the normal temperature group. These differences were even more striking in patients with an ISS ≥ 25. The very low temperature group had more penetrating trauma (11.6%) cases compared to the other groups. The overall mortality in our study population was 9.3% (n = 1,109). The crude mortality for each group is shown in Table 2. There was a significant increase in crude mortality across all temperature groups when compared to the normal temperature group ($p < 0.0001$).

The crude and adjusted odds of mortality in each group are shown in Table 2. The adjusted odds of mortality differed significantly in the very low temperature (aOR 2.41, 95% CI 1.83–3.17), low temperature (aOR 1.62, 95% CI 1.37–1.93), and elevated temperature (aOR 1.86, 95% CI 1.15–3.00) group as compared to the normal temperature group.

After excluding deaths, the association between ITCTs and crude non-mortality outcomes were calculated and are illustrated in Figure 2. This figure demonstrates the median hospital length of stay, ICU length of stay, and total hospital charges across all temperature groups. The median regression analysis provides the adjusted increases in median hospital length of stay, ICU length of stay, and TC total charges in all three groups compared with the normal temperature group (Table 3). All three groups had a significant increase in hospital length of stay and ICU length of stay compared to the normal temperature group (p values < 0.0001).

TABLE 2. Crude and adjusted odds of mortality when temperature on arrival to a trauma center is above or below normal

Temperature	Mortality n/N (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
>38°C	32/177 (18.0)	3.28 (2.21–4.86)	1.86 (1.15–3.00)
36.0–37.9°C	565/8971 (6.2)	Referent	Referent
35–35.9°C	365/2256 (9.5)	2.87 (2.49–3.30)	1.62 (1.37–1.93)
<35°C	147/473 (31.0)	6.70 (5.42–8.29)	2.41 (1.83–3.17)

DISCUSSION

The negative impact of secondary insults on TBI outcome is well known. For example, hypoxia,[9,10,12,17,38] hypotension,[9,12,16,17,38] and hyperventilation (in intubated patients)[14,15,38–40] are all associated with at least a doubling of mortality. While in-hospital fever is strongly associated with the risk of death,[31–33,36] a minimal amount is known regarding the impact of high temperatures occurring at the time of hospital arrival.

We found a significant association between abnormal initial trauma center temperature and poor outcomes in victims of major TBI. Since the temperatures were the initial ones obtained at the hospital, they likely reflect abnormalities that occurred during the prehospital interval. Although the association between hypothermia at the time of hospital arrival and increased mortality following TBI has been reported,[20,22,24,41,42] we believe this is the first study to demonstrate this association across the entire range of presenting temperatures. Our findings show that increased body temperature occurring during the prehospital interval has an associated increased risk that is similar to the other the commonly-reported secondary insults (i.e., hypoxia, hypotension, and hyperventilation). In addition to the mortality findings, we identified a strong association between abnormal ITCTs and non-mortality outcomes with statistically significant increases in hospital

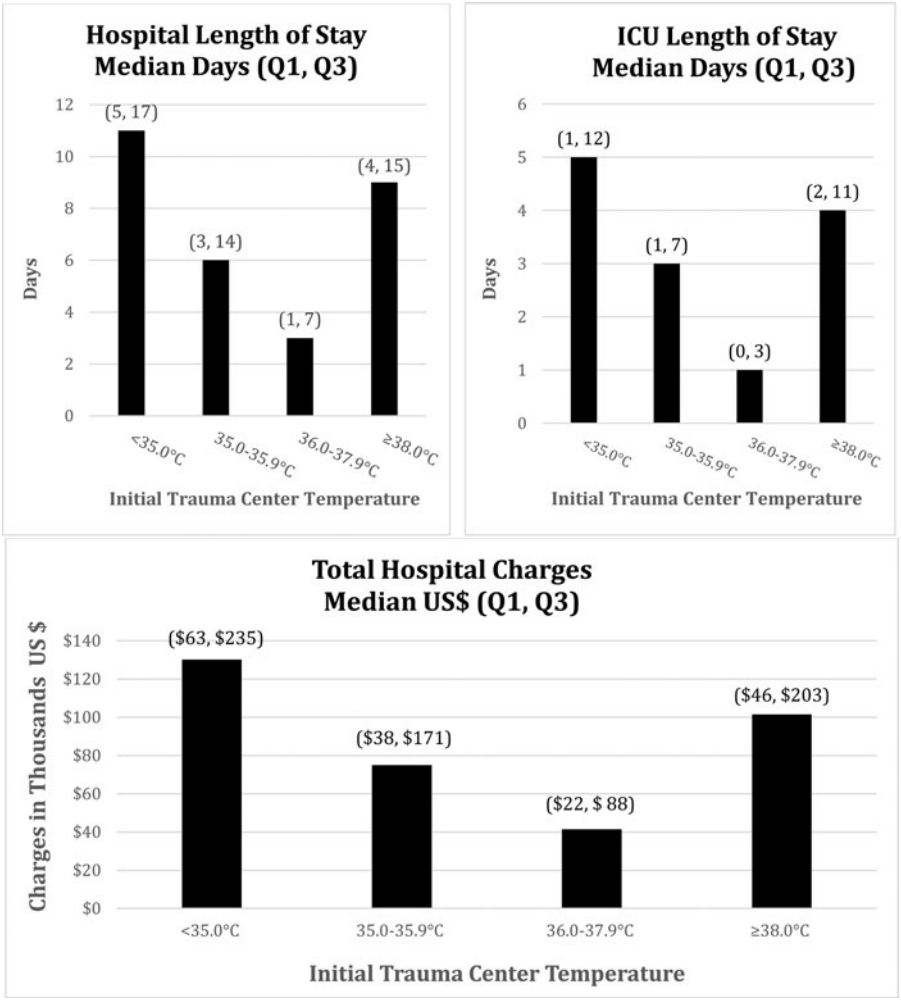

FIGURE 2. Unadjusted non-mortality outcomes by initial trauma center temperature. Values reported represent the raw or unadjusted median Hospital, ICU LOS, or hospital charges with (Q1 = 25th Percentile and Q3 = 75th percentile).

length of stay, ICU length of stay and hospital charges in patients with either high or low temperatures. We have been unable to find any previous studies that reported an association between alterations in body temperature and healthcare resource utilization.

The causes of the abnormal temperatures observed in this study remain unclear. In ICU settings, thermodysregulation or infection are common causes of temperature abnormalities in TBI patients.[31–33,36] In this study interfacility transfers were excluded and the vast majority of cases in the EPIC population arrive at the hospital less than 30 minutes after the injury. Thus, given the brief amount of time that transpires between the injury event and arrival at the trauma center, in the prehospital setting, variations in body temperature are much more likely to be caused by exposure to environmental temperature extremes rather than underlying pathophysiological processes.

The attempt to show a linkage between environmental conditions and body temperature in trauma patients has led to mixed results. One TBI study that evaluated environmental temperatures and patient outcomes demonstrated no association between them.[43] On the other hand, in both general trauma and TBI patients, some previous reports have demonstrated that the incidence of hypothermia is higher in the colder months of the year.[20,26] In addition, recent combat experience in Iraq and Afghanistan (predominantly warm climates) demonstrated that 7.4% of general trauma patients and as many as 47% of TBI patients had elevated temperatures on arrival at the forward aid stations.[41,44,45]

It is interesting that the prevalence of elevated temperatures in our study (177, 1.5%) was much lower than that of low temperatures (2256, 19.0%) or very low temperatures (473, 4.0%). Given the recent military literature described above and the relatively hot temperatures commonly encountered in Arizona (average summer high temperatures above 39°C), this finding was not anticipated. In part, this unexpected finding could be due to differences in injury location and prehospital care. For instance, civilian trauma patients

may be more likely to be injured inside air-conditioned vehicles and transported in air-conditioned ambulances. These factors could mitigate an initial exposure to high environmental temperatures or increase the incidence of low temperatures.

Patients in the low and very low temperature groups had a significant increase in the adjusted odds of mortality when compared to those with a normal temperature. This is not a new finding in trauma patients. However, the incidence of hypothermia after sustaining a moderate or severe TBI was surprisingly high. In fact, 23% of patients had an initial temperature <36.0°C. Thus, since environmental exposure may be a key cause of temperature variations that occur during the initial care of trauma patients, it appears that hypothermia should be avoided if at all possible in the prehospital setting.

Similarly in patients with elevated temperatures, there was a clear increase in mortality and in poor non-mortality outcomes. This, in conjunction with multiple ICU studies where hyperthermia was associated with poor outcomes, makes a compelling argument that variations in body temperature in either direction from normal should be avoided in TBI.

While there may be some validity to the current recommendations aimed at treating low and high temperatures in trauma patients, the design of our study does not allow us to make conclusions about the potential effectiveness of such treatment. However, these findings do support future study of the effectiveness of such treatment. Our findings supply an important reminder that, even under the optimal conditions in a controlled ICU setting, inadvertent occurrence of hypothermia or hyperthermia is common and poses significant risks to TBI patients. While in-hospital treatment of hypothermia has been associated with improved outcomes following injury, this has not been demonstrated in patients with elevated temperatures.[46] Therefore, any consideration of taking measures to prevent or treat body temperature abnormalities in the prehospital setting must carefully take into account the absence of demonstrated benefits and the potential risks. However, these finding do support future study of the effectiveness of such treatment and could help direct the future development of evidence-based guidelines for the field triage of patients with severe trauma.

LIMITATIONS

This study has several limitations. First, this is a retrospective, observational evaluation. Thus, it cannot be used to prove a causal effect of body temperature on outcome. Second, this study utilized CDC Barell Matrix among other criteria to identify patients with moderate or severe TBI. Use of diagnosis based inclusion criteria, may have introduced inclusion bias.[37,47] Additionally, by using this inclusion criteria, patients with other traumatic injuries were likely included in this study and the effect of temperature on TBI cannot be isolated. Third, we do not know whether there were attempts to treat body temperature either in the prehospital or trauma center environments. Thus, we are not able to identify associations with treatment. Finally, temperatures were recorded at 8 different trauma centers across the state and we are not able to determine the method, accuracy, or exact time of the measurements. Because this study assumes that ITCT was measured with the initial set of vital signs at the trauma center and patients without an ITCT were excluded, it is possible that other patient care activities took precedence over the measurement of body temperature and measurement of ITCT was delayed. Given that patients without a measured ITCT (excluded cases) had a higher ISS and were more likely to have penetrating trauma, this seems likely and may have introduced selection bias.

CONCLUSION

In this statewide study of major TBI, both low and high initial trauma center body temperatures were associated with a significant increase in severity adjust mortality and poor non-mortality outcomes. Future work is needed to identify the cause of prehospital body temperature variation in patients with TBI and whether initiation of in-field measures to prevent temperature abnormalities is safe and effective.

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Association of Out-of-Hospital Hypotension Depth and Duration With Traumatic Brain Injury Mortality

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Study objective: Out-of-hospital hypotension has been associated with increased mortality in traumatic brain injury. The association of traumatic brain injury mortality with the depth or duration of out-of-hospital hypotension is unknown. We evaluated the relationship between the depth and duration of out-of-hospital hypotension and mortality in major traumatic brain injury.

Methods: We evaluated adults and older children with moderate or severe traumatic brain injury in the preimplementation cohort of Arizona's statewide Excellence in Prehospital Injury Care study. We used logistic regression to determine the association between the depth-duration dose of hypotension (depth of systolic blood pressure <90 mm Hg integrated over duration [minutes] of hypotension) and odds of inhospital death, controlling for significant confounders.

Results: There were 7,521 traumatic brain injury cases included (70.6% male patients; median age 40 years [interquartile range 24 to 58]). Mortality was 7.8% (95% confidence interval [CI] 7.2% to 8.5%) among the 6,982 patients without hypotension (systolic blood pressure ≥90 mm Hg) and 33.4% (95% CI 29.4% to 37.6%) among the 539 hypotensive patients (systolic blood pressure <90 mm Hg). Mortality was higher with increased hypotension dose: 0.01 to 14.99 mm Hg-minutes 16.3%; 15 to 49.99 mm Hg-minutes 28.1%; 50 to 141.99 mm Hg-minutes 38.8%; and greater than or equal to 142 mm Hg-minutes 50.4%. Log_2 (the logarithm in base 2) of hypotension dose was associated with traumatic brain injury mortality (adjusted odds ratio 1.19 [95% CI 1.14 to 1.25] per 2-fold increase of dose).

Conclusion: In this study, the depth and duration of out-of-hospital hypotension were associated with increased traumatic brain injury mortality. Assessments linking out-of-hospital blood pressure with traumatic brain injury outcomes should consider both depth and duration of hypotension. [Ann Emerg Med. 2017;70:522-530.]

Please see page 523 for the Editor's Capsule Summary of this article.

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SEE EDITORIAL, 531.

INTRODUCTION

Background

During the out-of-hospital and early inhospital resuscitative care of traumatic brain injury, hypotension is associated with increased mortality.[1-31] The literature supporting this concept is based on small series with only limited emergency medical services (EMS) data that characterized hypotension dichotomously (<90 or ≥90 mm Hg).[3,16,21,28-31] Thus, very little is known about the effect of the depth of hypotension. Another limitation of these studies is the absence of repeated blood pressure measurements. Because of this, there are no descriptions of the depth and duration of out-of-hospital hypotension in traumatic brain injury patients, to our knowledge.

Importance

Hypotension is believed to reduce cerebral perfusion pressure to the injured brain.[4,6,11,26,32] Although not yet characterized, the extent of brain injury is likely linked to both the depth and duration of hypotensive episodes. Quantification of hypotension dose could offer an additional therapeutic target for refining out-of-hospital traumatic brain injury care.

Goals of This Investigation

The objective of this study was to determine the association of out-of-hospital hypotension depth and duration with traumatic brain injury mortality.

Editor's Capsule Summary

What is already known on this topic

Out-of-hospital hypotension (systolic blood pressure <90 mm Hg) is associated with poor traumatic brain injury outcomes.

What question this study addressed

Are out-of-hospital hypotension duration and depth associated with traumatic brain injury outcomes?

What this study adds to our knowledge

In this study of 7,521 traumatic brain injuries in Arizona, each 2-fold increase in out-of-hospital hypotension dose (hypotension depth integrated across exposure time) was associated with a 20% increase in mortality.

How this is relevant to clinical practice

Traumatic brain injury research and clinical strategies should consider both hypotension depth and duration.

MATERIALS AND METHODS

Setting

Details of the Excellence in Prehospital Injury Care (EPIC) study have been described previously.[33-35] The study is evaluating the effect of implementing the EMS traumatic brain injury guidelines[36-39] in patients with major traumatic brain injury throughout Arizona, using a before-after, controlled, multisystem, observational design.[33] We obtained the necessary regulatory approvals for the study from the Arizona Department of Health Services and the state attorney general. The University of Arizona Institutional Review Board and the Arizona Department of Health Services Human Subjects Review Board have approved the project and have determined that, by virtue of being a public health initiative, neither the interventions nor their evaluation constitutes human subjects research and have approved the publication of deidentified data.

Selection of Participants

The patients in this evaluation were in the preimplementation cohort of the EPIC study (treated by an EMS agency between January 1, 2007, and March 31, 2014, without receiving study interventions). In this secondary analysis, we included patients aged 10 years or older with physical trauma who had trauma center diagnoses consistent with traumatic brain injury (isolated or multisystem trauma) and met at least one of the following definitions for moderate or severe ("major") traumatic brain injury: Centers for Disease Control and Prevention Barell Matrix-type 1, *International Classification of Diseases, Ninth Revision (ICD-9)* head region severity score greater than or equal to 3, and Abbreviated Injury Score greater than or equal to 3 for the head region.[33,34] We excluded cases with age younger than 10 years; interfacility transfer (or unknown); any systolic blood pressure greater than 200 mm Hg; systolic blood pressure 0, indicating traumatic arrest; missing important confounders or risk adjusters; and zero or only one recorded out-of-hospital systolic blood pressure with documented time between 6 hours before emergency department (ED) arrival and 10 minutes after ED arrival (excludes extreme or obviously inaccurate time data). The patients with only one timed, recorded systolic blood pressure measurement were excluded because at least 2 are needed to establish depth-duration dose.

Methods of Measurement

The EPIC database contains the subset of patients from the Arizona State Trauma Registry meeting EPIC study criteria for major traumatic brain injury (defined above).[33-35] The registry has detailed inhospital data on all trauma patients taken to the state-designated Level I trauma centers in Arizona. All cases from the registry that meet the EPIC study criteria are entered into the database. Each participating EMS agency receives the list of study patients cared for in their system. The cases are matched by incident date, name, and other identifiers. Either scanned copies (paper-based patient care records) or electronic data files are sent to the EPIC data center. Database personnel then comprehensively abstract and enter the data, yielding an extensive, linked data set that includes both EMS and trauma center data. The processes of case identification, linkage, data entry, and data quality management have been reported in detail.[33] We have enrolled more than 20,000 cases into the EPIC study, and the Arizona State Trauma Registry and EMS data linkage rate is well over 90%.

We included all systolic blood pressure measurements with a recorded value and time. When multiple agencies cared for a given patient, we combined all available measurements. Patients who had at least 2 timed systolic blood pressure measurements were included in this analysis. We excluded cases with only one recorded systolic blood pressure measurement because the duration of hypotension could not be accurately estimated.

Our strategy for determining hypotension dosage was modeled after pharmacokinetic techniques.[40] We defined hypotension depth duration as the total amount of systolic hypotension (systolic blood pressure <90 mm Hg)

accumulated during a given time. Hypotensive depth referred to the difference between 90 mm Hg and the measured value. Duration referred to the total time during which systolic blood pressure was less than 90 mm Hg. To calculate the depth-duration dose, we linked consecutive systolic blood pressure measurements over time, calculating hypotension dose as the integrated "area under the curve" for values less than 90 mm Hg (Figure 1). In situations with multiple separate hypotensive episodes, we added the integrated values from all hypotensive segments (Figure 2).

Outcome Measures

The primary outcome was survival to hospital discharge.[33] Deaths that occurred after hospital discharge were not included in the analysis.

Primary Data Analysis

We determined traumatic brain injury mortality for the cohort and the quartile of hypotension dose. We then examined the association between mortality and dose by logistic regression, adjusting for potential confounders. Age, sex, race, ethnicity, Injury Severity Score, and head region injury score (*ICD-9* matched to Abbreviated Injury Score)[41-43] were included a priori in the model (because they have been used nearly universally in trauma risk adjustment). Trauma type (blunt versus penetrating), payment source, and treating trauma center were included because they have often been confounders in trauma outcome studies[44,45] and were found to be significant covariates in previous EPIC reports.[34,35]

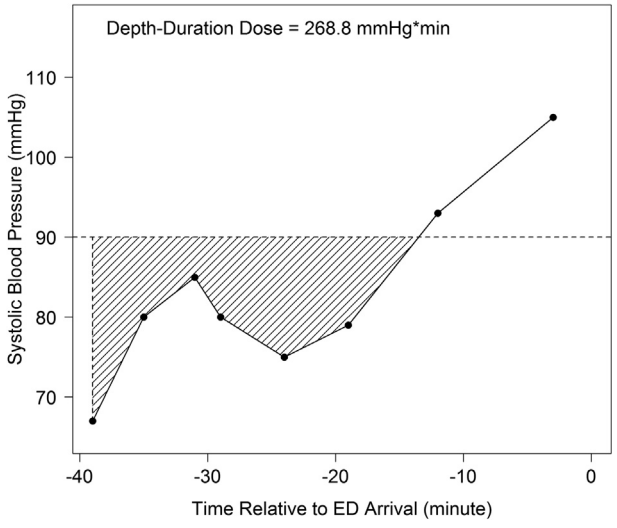

Figure 1. Depth-duration dose plot from a study patient. Depth-duration dose=total area of the shaded region under 90 mm Hg. When the dose is calculated, if either the first (as in this case) or last recorded SBP is a hypotensive value, the shaded region is closed by a vertical line passing through this point.

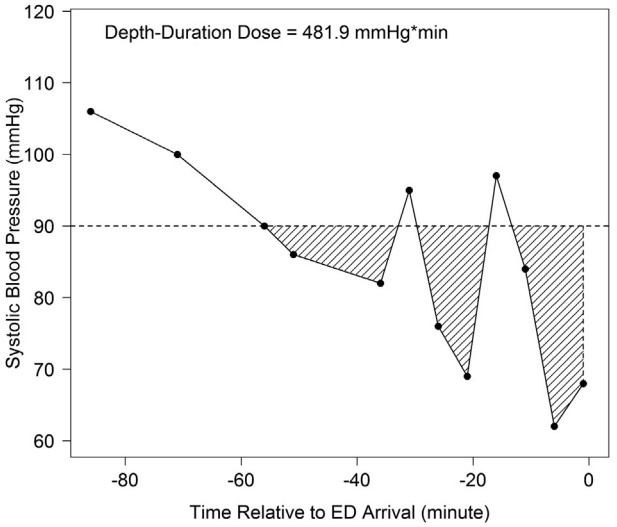

Figure 2. Depth-duration dose plot from a study patient with multiple hypotensive episodes. Depth-duration dose=total area of the shaded region under 90 mm Hg. When the dose is calculated, if either the first or last (as in this case) recorded SBP is a hypotensive value, the shaded region is closed by a vertical line passing through this point. This case shows a patient with 3 separate hypotensive episodes in which the total dose is the sum of the AUC from all of the shaded regions.

Because of the skewed distribution of hypotension dose, we log-transformed hypotension dose ($\log_2$[dose+1]). This approach yielded a value of 0 for patients without hypotension and positive values for hypotensive cases. The effects of the $\log_2$ hypotension dose and age in the regression were fitted nonparametrically with penalized thin-plate regression splines through the generalized additive model,[46] with the smoothing parameter chosen to optimize the Akaike information criterion. Nested models were compared with an analysis of deviance table. We assessed the fitted model by deviance residual plots and the area under the receiver operating characteristic curve (AUC) with 95% confidence interval (CI) obtained by the DeLong method.[47] We checked for collinearity with variance inflation factors for the parametric terms and concurvity for the nonparametric term. Mixed-effect models were used to assess the effect of the correlation of subjects treated by the same trauma center.

We evaluated the predictive power of the hypotension dose by first fitting a logistic regression model for survival with demographic variables as predictors (model 1), then adding the binary hypotensive indicator (<90 or ≥90 mm Hg) as another predictor (model 2), and then adding dose ($\log_2$[hypotension dose+1]) (model 3). The AUC was estimated for each model. We further evaluated predictive power by comparing different models, using the

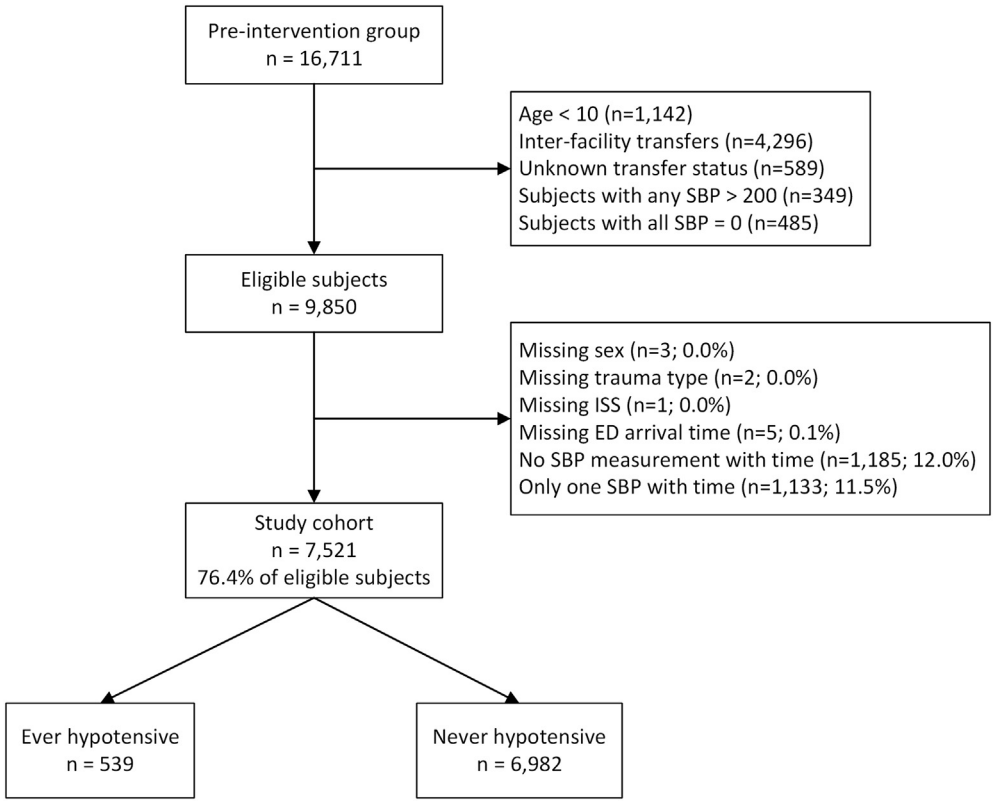

Figure 3. Case inclusion/exclusion flow chart. *SBP*, Systolic blood pressure; *ISS*, Injury Severity Score.

continuous net reclassification improvement,[48] with 95% CI estimated by the bootstrap method.

We used the software environment R for the analysis[49] and the R package mgcv[46,50] for the generalized additive model.

RESULTS

Among 16,711 traumatic brain injury subjects, we included 7,521 in the analysis (Figure 3). Median age was 40 years (interquartile range 24 to 57), 70.6% were men, and overall mortality was 9.6% (95% CI 9.0% to 10.3%). In the study group, 539 patients (7.2%) had hypotension. Among patients with no hypotension, 7.8% died (95% CI 7.2% to 8.5%) compared with 33.4% (95% CI 29.4% to 37.6%) in the group with at least one hypotensive episode. Demographics and patient characteristics are shown in Table 1 (by hypotension status) and Appendix E1, available online at http://www.annemergmed.com (by survival status). Figure 4 shows the distribution of depth, duration, and dose among the 539 hypotensive patients. All factors associated with hypotension status were also associated with risk of death (trauma type, head region injury score, Injury Severity Score, and out-of-hospital hypoxia), whereas age and payment source were associated with death but not hypotension status. As with previous reports, risk-adjusted outcomes varied among trauma centers.[44,45] Thus, we adjusted for it in the model.

The unadjusted probability of death increased with higher hypotension dose (Figure 5). We used logistic regression to examine the association between $\log_2$ dose and the risk of death, controlling for potential confounders, with the effects of the continuous variables ($\log_2$ dose and age) modeled as nonparametric functions. We observed a monotonically increasing linear relationship between $\log_2$ dose and log odds of death (adjusted odds ratio [OR]=1.19; 95% CI 1.14 to 1.25) per 2-fold hypotension dose increase) (Table 2, Figure 6).

Deviance residual plots did not indicate any deviation from the model assumptions. The effect of dose (after transformation), when fitted as a nonparametric function, was not statistically different from a simple linear function. The AUC was estimated to be 0.952 (95% CI 0.945 to 0.958), indicating a high discriminative ability of the model. No multicollinearity was detected in the covariates.

As a sensitivity analysis, random trauma center effects were included in the model (instead of fixed effects) to explore the potential correlation among subjects treated by the same trauma center. The differences were minimal,

Table 1. Patient characteristics by hypotension status.

Group	Never Hypotensive*†	Ever Hypotensive*†
No. of subjects	6,982	539
Age, y	40 (24–58)	37 (23–55)
Male patient		
No	2,047 (29.3)	161 (29.9)
Yes	4,935 (70.7)	378 (70.1)
Race		
Black	234 (3.4)	10 (1.9)
Asian	68 (1)	8 (1.5)
American Indian/Alaska Native	388 (5.6)	39 (7.2)
White	5,373 (77)	412 (76.4)
Other	843 (12.1)	59 (10.9)
Unknown	76 (1.1)	11 (2)
Hispanic		
No	5,256 (75.3)	400 (74.2)
Yes	1,512 (21.7)	114 (21.2)
Unknown	214 (3.1)	25 (4.6)
Payer		
Private	2,593 (37.1)	196 (36.4)
AHCCCS/Medicaid	1,805 (25.9)	154 (28.6)
Medicare	1,062 (15.2)	64 (11.9)
Self-pay	1,084 (15.5)	84 (15.6)
Other	299 (4.3)	26 (4.8)
Unknown	139 (2)	15 (2.8)
Trauma type		
Blunt	6,685 (95.7)	463 (85.9)
Penetrating	297 (4.3)	76 (14.1)
Head Region Severity Score *(ICD-9)*		
1–3	4,043 (57.9)	207 (38.4)
4	1,835 (26.3)	110 (20.4)
5–6	1,027 (14.7)	209 (38.8)
Unknown	77 (1.1)	13 (2.4)
ISS *(ICD-9)*		
1–14	2,954 (42.3)	81 (15)
16–24	2,147 (30.8)	100 (18.6)
≥25	1,881 (26.9)	358 (66.4)
Hypotension dose (mm Hg-min)	0 (0–0)	49 (15–142.5)
Out-of-hospital hypoxia		
No	6,205 (88.9)	348 (64.6)
Yes	480 (6.9)	147 (27.3)
Unknown	297 (4.3)	44 (8.2)

AHCCCS, Arizona Health Care Cost Containment System.
*Median (interquartile range) for continuous variables and count (percentage) for categorical variables.
†Hypotension defined as systolic blood pressure less than 90 mm Hg.

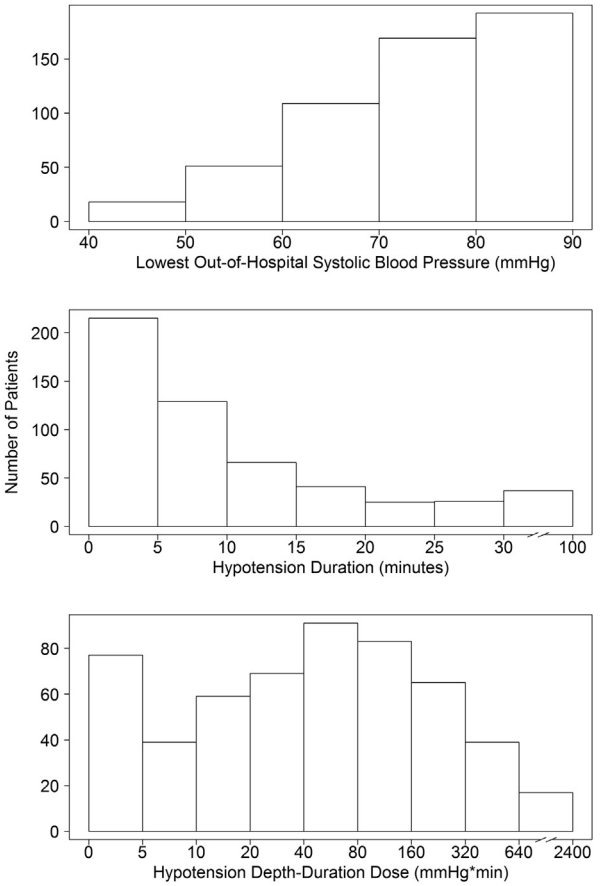

Figure 4. Distribution of hypotension depth, duration, and dose across the hypotensive cohort. Histograms show the proportions of hypotensive patients by depth, duration, and dose of hypotension.

with a change in the estimated OR for $\log_2$ dose of only 0.1% and in the standard error estimate for the corresponding regression coefficient of only 0.5%. Among the 8 trauma centers, there was an average of 940 subjects per site and the intraclass correlation coefficient for the trauma center effect was 0.066. In a separate sensitivity analysis, instead of $\log_2$ hypotension dose we included the standardized hypotension dose (dose minus the sample mean and then divided by the SD) in the logistic regression. The resulting inferences were similar (adjusted OR 1.27 per SD increase in hypotension dose; 95% CI 1.17 to 1.37) (Appendix E2, available online at http://www.annemergmed.com).

In a model with only basic demographic variables as predictors, the AUC was 0.585 (95% CI 0.563 to 0.607). Adding binary hypotension (systolic blood pressure <90 versus ≥90 mm Hg) improved AUC to 0.6635 (95% CI 0.6409 to 0.6860) and the net reclassification improvement was 39.1% (95% CI 32.5% to 45.5%). When hypotension dose ($\log_2$[dose+1]) was added to the binary model, the AUC improved slightly to 0.6638 (95% CI 0.6411 to 0.6865); the net reclassification improvement was 8.1% (95% CI –5.6% to 21.8%) for the dose-based model over the binary model. When the analysis was limited to the 539 subjects with hypotension, the basic model had an AUC of 0.616 (95% CI 0.566 to 0.666). Addition of hypotension dose improved AUC to 0.707 (95% CI 0.659 to 0.754), and the net reclassification improvement was 47.5% (95% CI 27.5% to 69.8%).

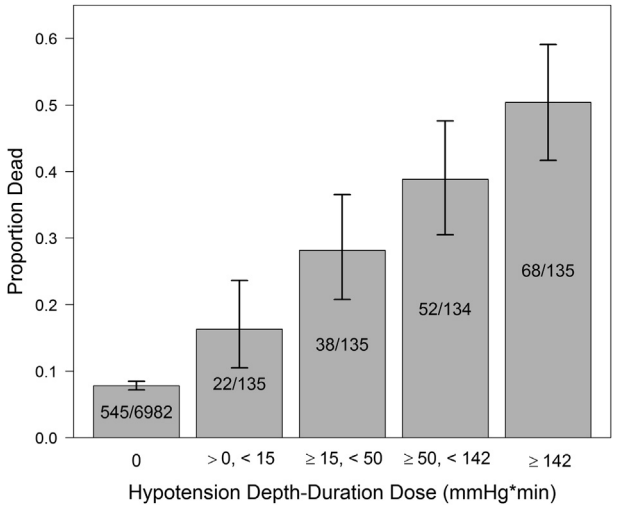

Figure 5. Unadjusted death proportion by hypotension dose categories. Error bars represent 95% CIs. Hypotension was defined as systolic blood pressure less than 90 mm Hg.

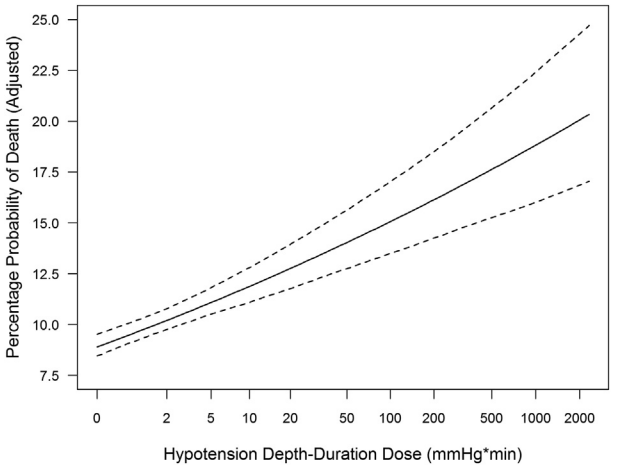

Figure 6. Relationship of hypotension depth-duration dose to adjusted probability of death. Dotted lines represent pointwise 95% confidence band. Hypotension was defined as systolic blood pressure less than 90 mm Hg. *x* axis is $\log_2$ scale.

Table 2. Logistic regression model for survival status.

Variable*	Category	OR†	95% CI
log2(SBP dose+1)	NA	1.19	(1.14–1.25)
Male patient	No	[Reference]	[Reference]
	Yes	0.95	(0.74–1.21)
Race	Black	[Reference]	[Reference]
	Asian	1.77	(0.51–6.15)
	American Indian/ Alaska Native	2.07	(0.92–4.65)
	White	2.33	(1.19–4.57)
	Other	2.38	(1.08–5.24)
	Unknown	3.41	(1.14–10.23)
Hispanic	No	[Reference]	[Reference]
	Yes	0.55	(0.39–0.79)
	Unknown	1.43	(0.78–2.60)
Payer	Private	[Reference]	[Reference]
	AHCCCS/Medicaid	0.95	(0.71–1.29)
	Medicare	1.16	(0.78–1.74)
	Self-pay	3.27	(2.31–4.61)
	Other	1.56	(0.95–2.57)
	Unknown	2.86	(1.44–5.65)
Trauma type	Blunt	[Reference]	[Reference]
	Penetrating	4.96	(3.54–6.95)
Head region severity score *(ICD-9)*	1–3	[Reference]	[Reference]
	4	1.17	(0.77–1.78)
	5–6	14.21	(9.64–20.96)
	Unknown	6.29	(2.70–14.64)
ISS *(ICD-9)*	1–14	[Reference]	[Reference]
	16–24	4.92	(2.18–11.09)
	≥25	23.58	(10.88–51.11)
Out-of-hospital hypoxia	No	[Reference]	[Reference]
	Yes	2.47	(1.88–3.24)
	Unknown	2.91	(1.96–4.31)
Age	Fitted nonparametrically		

*Also adjusted for treating trauma centers (details not shown).
†OR for death associated with 1-unit increase in continuous variable or compared with the referent category for categorical variables.

LIMITATIONS

This study has limitations. The design is observational, and thus we could not determine whether the treatment of hypotension effectively reduced mortality (this hypothesis is part of the main study). However, this analysis did allow us, for the first time, to identify significant associations between the dose of hypotension and outcome.

There are missing data. Although the missing rate for EMS systolic blood pressure measurements is very low (<5%),[51] the addition of the requirement for 2 timed systolic blood pressure measurements for this analysis led to a rate of 23.6% (Figure 3). The database contains only measurements that were documented by EMS personnel, and we cannot independently verify their accuracy. However, the data are abstracted directly, consistently, and comprehensively from the patient care records. This level of data collection scrutiny is rare in EMS research.[51]

The hypotension dose estimate is affected by how frequently blood pressure was measured. Indeed, we found that a low measurement was more likely to be repeated quickly, which would lead to a more accurate estimation of the dose. However, the fact that nonhypotensive values tended to lead to fewer repeated measurements is not likely to have significantly affected our findings because the dose in nonhypotensive patients is zero regardless of how many times blood pressure was measured. Finally, we did not evaluate the effects of treatment. Future studies will assess the influence of traumatic brain injury care on outcomes.

DISCUSSION

It is well established that out-of-hospital hypotension is associated with increased traumatic brain injury

mortality.[3,16,21,28-31,34,38,52] However, the literature that has shaped this understanding has evaluated hypotension as a simple dichotomy (<90 or ≥90 mm Hg).[3,16,21,28-31,38] To our knowledge, currently there are no published reports with data evaluating the effect of either the depth or the duration of out-of-hospital hypotension. The paucity of knowledge related to these parameters in the field is reflected in the most recent EMS traumatic brain injury treatment guidelines, which state that a major area needing investigation is identifying "the critical values for duration and magnitude of hypotensive…episodes."[38,53] Our study offers one of the first assessments of the association between hypotension dose and traumatic brain injury outcomes. These findings add to the increasing evidence that close and frequent blood pressure monitoring and management may contribute to improved traumatic brain injury outcomes.[4,7,8,15,23,30,32,33,36,38]

The EPIC database contains all vital signs measurements and their associated times that are recorded on the EMS patient care records. The data entry system allows an unlimited number of data entries for vital signs.[33,34] In fact, in this substudy, there are patients with as many as 25 EMS blood pressure measurements recorded in the database, and the median number is 4 per patient. This feature allows the plotting of out-of-hospital blood pressure over time and, hence, an estimation of the depth and duration of hypotensive events (Figures 1 and 2). These strengths allowed us to evaluate the hypotension dose as a novel measure.

Our study affirmed the presence of a dose-response association between hypotension dosage and mortality. The simple, unadjusted mortality rate increased significantly and consistently across the 4 quartiles (by dose) of hypotensive patients (Figure 5). Furthermore, a doubling of dose was associated with an adjusted OR for death of 1.19, and this association held over a wide range of hypotension doses (Figure 6). Thus, with other factors being equal, in hypotensive traumatic brain injury patients, a doubling of dose yielded a 19% increase in adjusted odds of death. For example, a patient in whom systolic blood pressure decreases to 80 mm Hg for 10 minutes (dose=100 mm Hg-minutes) has 19% higher odds of dying than one with a dose of only 50 mm Hg-minute (eg, 85 mm Hg for 10 minutes or 80 mm Hg for 5 minutes). Our findings not only provide evidence for the face validity of the dose-duration construct but also may support the notion of minimizing both hypotension depth and duration during clinical care.

Our findings did not show a marked improvement in model discrimination or net reclassification improvement for the hypotensive dosage model compared with the binary hypotension model in the overall study group. However, we believe this was predictable because 92.8% of the subjects were nonhypotensive. Hence, this comparison is dominated by the nonhypotensive patients, and only small improvement is expected when the entire study group is evaluated no matter how well the dose model discriminates between hypotensive patients. On the other hand, in the assessment of the hypotensive cohort, the binary model becomes moot because all patients in this subgroup have the same value (positive for hypotension) and, unlike depth-duration dose, it has no discriminative value among hypotensive patients. The implementation phase of the larger EPIC study is applying the evidence-based guidelines for out-of-hospital traumatic brain injury care. We plan to use the postimplementation cases not only to validate the current findings but also to identify alternate functional forms with clearer improvement of the dosage-based model over binary hypotension. For instance, because our previous work revealed a complete absence of an identifiable physiologic threshold anywhere between a systolic blood pressure of 40 and 120 mm Hg,[35] the discriminatory power of the model may improve when hypotension is defined as less than 100, less than 110, or less than 120 mm Hg.[53] Furthermore, when higher thresholds are evaluated, comparing the binary model versus the dose-based model in the overall study cohort will be pertinent because such a comparison will be much less likely to be dominated by the nonhypotensive subgroup. We will also be able to explore questions such as whether it is better to be less hypotensive longer or more hypotensive for a shorter time. The current study underscores the importance of hypotension dosage in traumatic brain injury care and sets the stage for these future analyses.

Another important consideration is how to implement these findings into EMS practice. We hesitate to recommend specific measures until additional validation has identified the most accurate model. However, our results do identify the technical challenges at hand. Calculation of hypotension dosage requires real-time computer decision support. Current portable cardiac monitors are able to give real-time feedback such as cardiopulmonary resuscitation chest compression rate, depth, and fraction.[54] Future efforts must consider the technologic support required to implement the new measure in traumatic brain injury patients.

In summary, this statewide, multisystem study of major traumatic brain injury found that the depth and duration of out-of-hospital hypotension were strongly associated with increased mortality. Assessments linking out-of-hospital blood pressure with traumatic brain injury outcomes should account for both the depth and duration of hypotension.

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Appendix E1. Patient characteristics by survival status.

Group	Lived*	Died*
No. of subjects	6,796	725
Age, y	40 (24–57)	44 (26–65)
Male patient		
No	2,016 (29.7)	192 (26.5)
Yes	4,780 (70.3)	533 (73.5)
Race		
Black	226 (3.3)	18 (2.5)
Asian	70 (1)	6 (0.8)
American Indian/Alaska Native	391 (5.8)	36 (5)
White	5,228 (76.9)	557 (76.8)
Other	811 (11.9)	91 (12.6)
Unknown	70 (1)	17 (2.3)
Hispanic		
No	5,116 (75.3)	540 (74.5)
Yes	1,482 (21.8)	144 (19.9)
Unknown	198 (2.9)	41 (5.7)
Payer		
Private	2,591 (38.1)	198 (27.3)
AHCCCS/Medicaid	1,804 (26.5)	155 (21.4)
Medicare	980 (14.4)	146 (20.1)
Self-pay	1,011 (14.9)	157 (21.7)
Other	286 (4.2)	39 (5.4)
Unknown	124 (1.8)	30 (4.1)
Trauma type		
Blunt	6,602 (97.1)	546 (75.3)
Penetrating	194 (2.9)	179 (24.7)
Head Region Severity Score ISS *(ICD-9)*		
1–3	4,202 (61.8)	48 (6.6)
4	1,875 (27.6)	70 (9.7)
5–6	640 (9.4)	596 (82.2)
Unknown	79 (1.2)	11 (1.5)
ISS *(ICD-9)*		
1–14	3,026 (44.5)	9 (1.2)
16–24	2,209 (32.5)	38 (5.2)
≥25	1,561 (23)	678 (93.5)
Any exposure to low SBP†		
No	6,437 (94.7)	545 (75.2)
Yes	359 (5.3)	180 (24.8)
Out-of-hospital hypoxia		
No	6,125 (90.1)	428 (59)
Yes	416 (6.1)	211 (29.1)
Unknown	255 (3.8)	86 (11.9)

*Lived=survived to hospital discharge. Died=died in the hospital. Median (interquartile range) for continuous variables and count (percentage) for categorical variables.
†Hypotension defined as SBP less than 90 mm Hg.

Appendix E2. Logistic regression model for survival status with standardized hypotension dose.

Variable*	Category	OR†	95% CI
Standardized hypotension dose	NA	1.27	(1.17–1.37)
Male patient	No	[Reference]	[Reference]
	Yes	0.93	(0.73–1.18)
Race	Black	[Reference]	[Reference]
	Asian	2.19	(0.65–7.39)
	American Indian/Alaska Native	2.25	(1.01–5.03)
	White	2.45	(1.26–4.79)
	Other	2.47	(1.13–5.42)
	Unknown	3.49	(1.17–10.39)
Hispanic	No	[Reference]	[Reference]
	Yes	0.56	(0.40–0.80)
	Unknown	1.52	(0.85–2.75)
Payer	Private	[Reference]	[Reference]
	AHCCCS/Medicaid	0.96	(0.71–1.29)
	Medicare	1.17	(0.79–1.75)
	Self-pay	3.28	(2.32–4.62)
	Other	1.56	(0.95–2.56)
	Unknown	2.91	(1.48–5.71)
Trauma type	Blunt	[Reference]	[Reference]
	Penetrating	5.15	(3.68–7.20)
Head region severity score *(ICD-9)*	1–3	[Reference]	[Reference]
	4	1.21	(0.79–1.85)
	5–6	15	(10.09–22.30)
	Unknown	7.08	(3.04–16.50)
ISS *(ICD-9)*	1–14	[Reference]	[Reference]
	16–24	4.95	(2.20–11.16)
	≥25	23.41	(10.80–50.75)
Out-of-hospital hypoxia	No	[Reference]	[Reference]
	Yes	2.6	(1.98–3.41)
	Unknown	2.88	(1.94–4.27)
Age	Fitted nonparametrically		

*Also adjusted for treating trauma centers (details not shown).
†OR for death associated with 1-unit increase in continuous variable or compared with the referent category for categorical variables.

The Effect of Combined Out-of-Hospital Hypotension and Hypoxia on Mortality in Major Traumatic Brain Injury

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Study objective: Survival is significantly reduced by either hypotension or hypoxia during the out-of-hospital management of major traumatic brain injury. However, only a handful of small studies have investigated the influence of the combination of both hypotension and hypoxia occurring together. In patients with major traumatic brain injury, we evaluate the associations between mortality and out-of-hospital hypotension and hypoxia separately and in combination.

Methods: All moderate or severe traumatic brain injury cases in the preimplementation cohort of the Excellence in Prehospital Injury Care study (a statewide, before/after, controlled study of the effect of implementing the out-of-hospital traumatic brain injury treatment guidelines) from January 1, 2007, to March 31, 2014, were evaluated (exclusions: <10 years, out-of-hospital oxygen saturation ≤10%, and out-of-hospital systolic blood pressure <40 or >200 mm Hg). The relationship between mortality and hypotension (systolic blood pressure <90 mm Hg) or hypoxia (saturation <90%) was assessed with multivariable logistic regression, controlling for Injury Severity Score, head region severity, injury type (blunt versus penetrating), age, sex, race, ethnicity, payer, interhospital transfer, and trauma center.

Results: Among the 13,151 patients who met inclusion criteria (median age 45 years; 68.6% men), 11,545 (87.8%) had neither hypotension nor hypoxia, 604 (4.6%) had hypotension only, 790 (6.0%) had hypoxia only, and 212 (1.6%) had both hypotension and hypoxia. Mortality for the 4 study cohorts was 5.6%, 20.7%, 28.1%, and 43.9%, respectively. The crude and adjusted odds ratios for death within the cohorts, using the patients with neither hypotension nor hypoxia as the reference, were 4.4 and 2.5, 6.6 and 3.0, and 13.2 and 6.1, respectively. Evaluation for an interaction between hypotension and hypoxia revealed that the effects were additive on the log odds of death.

Conclusion: In this statewide analysis of major traumatic brain injury, combined out-of-hospital hypotension and hypoxia were associated with significantly increased mortality. This effect on survival persisted even after controlling for multiple potential confounders. In fact, the adjusted odds of death for patients with both hypotension and hypoxia were more than 2 times greater than for those with either hypotension or hypoxia alone. These findings seem supportive of the emphasis on aggressive prevention and treatment of hypotension and hypoxia reflected in the current emergency medical services traumatic brain injury treatment guidelines but clearly reveal the need for further study to determine their influence on outcome. [Ann Emerg Med. 2017;69:62-72.]

Please see page 63 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background and Importance

Traumatic brain injury is a massive public health problem, leading to more than 50,000 deaths and enormous health care expenditures each year in the United States.[1,2] The Centers for Disease Control and Prevention (CDC) estimates that at least 5.3 million Americans, approximately 2% of the US population, are living with a major, permanent, traumatic brain injury–related disability.[2,3]

During the out-of-hospital care of patients with traumatic brain injury, hypoxia occurs frequently[4-9] and significantly increases mortality.[6,7,10-16] It is independently associated with a higher risk of death even if the hypoxemic episode is reflected by only a single measurement of low

Editor's Capsule Summary

What is already known on this topic

Both hypotension and hypoxia are independently associated with higher mortality among out-of-hospital patients with traumatic brain injury.

What question this study addressed

For out-of-hospital patients with traumatic brain injury, what is the effect on survival of the combination of hypotension and hypoxia compared with either factor alone?

What this study adds to our knowledge

Among 13,151 out-of-hospital patients with traumatic brain injury during a 7-year period, only 1.6% experienced both hypotension and hypoxia. Mortality was 5.6% for patients with neither but 43.9% when the combination of hypotension and hypoxia occurred. The adjusted odds ratio for death was 6.1 (95% confidence interval [CI] 4.2 to 8.9) for the combination, 2.5 (95% CI 1.9 to 3.3) for hypotension alone, and 3.0 (95% CI 2.4 to 3.8) for hypoxia alone.

How this is relevant to clinical practice

Emphasis should be placed on avoiding hypotension and hypoxia in patients with traumatic brain injury, and additional attention should be paid to preventing their combination.

oxygen saturation.[10,12,17] Stocchetti found that the presence of out-of-hospital hypoxia more than tripled the likelihood of death among victims of severe traumatic brain injury.[6] Hypotension is also very common early in the care of traumatic brain injury[7,10,11,18] and significantly affects survival.[6,10,11,14,15,18-39] A single episode of hypotension doubles mortality, and this risk increases significantly with repeated episodes (an odds ratio [OR] of 8.1 for death in one study).[26]

Although the negative effect of hypotension and hypoxia has been well documented in the literature, little is known about their combination. Thus, it is unknown whether, together, they have no additional effect, an additive effect, or some intermediate influence on outcomes. Even though it is known that hypotension and hypoxia independently increase mortality, this is not the same as showing that the combination of the two is additive in its effect in patients who actually experience both. In fact, some authors have suggested that, because there are great similarities at the cellular level in the effect of hypoxia and hypotension (reduced oxygen delivery to the neuron), having both may add little to the risk of death because the physiologic insult may be similar with either or both.[16,22,26] With the exception of a meta-analysis that had major issues with study heterogeneity and missing data,[39] the reports that have examined the effect of hypotension combined with hypoxia in traumatic brain injury have included few cases.[6,16,22,26,28,35,40] Furthermore, even less is known about this problem in the out-of-hospital setting. To our knowledge, only 2 previous studies specifically evaluated the hypotension and hypoxia combination with out-of-hospital data.[6,16] A key reason for evaluating the effect of blood pressure and oxygenation measured before hospital arrival is because the injured brain is so highly sensitive to changes in perfusion and oxygenation and the timeframe during which neuronal damage begins is so short. It is well established that secondary brain injury is initiated by even brief periods of compromised blood flow or hypoxia.[20,22,23,28,35,40-43] Thus, decreased perfusion or hypoxia occurring during the out-of-hospital interval may have a profound effect on outcome.

Goals of This Investigation

The objective of this investigation was to evaluate the association between survival and out-of-hospital hypotension, hypoxia, or both in patients with major traumatic brain injury.[41]

In major traumatic brain injury, the combination of both out-of-hospital hypotension (systolic blood pressure <90 mm Hg) and hypoxia (oxygen saturation <90%) has additional negative influence on survival compared with either factor alone.

MATERIALS AND METHODS

The Excellence in Prehospital Injury Care (EPIC) study has been described in detail elsewhere.[41] It is funded by the National Institutes of Health, and, although not a randomized trial, it is registered at ClinicalTrials.gov (NCT01339702). Rather than reiterating the details of the parent study, here we limit the description to the design attributes relevant to this specific evaluation.

Setting

The EPIC study is evaluating the effect of implementing the out-of-hospital traumatic brain injury guidelines[42-45] in patients with moderate or severe ("major") traumatic brain injury throughout Arizona, using a before-after, controlled, multisystem, observational design. The patients in this evaluation are in the preimplementation cohort of EPIC (treated by an emergency medical services [EMS] agency between January 1, 2007, and March 31, 2014, without

receiving EPIC study interventions). Cases in the interventional cohort were excluded for 2 reasons. First, inclusion of postintervention cases in this observational evaluation would encroach on several of the main hypotheses of the primary parent study, and the analysis plan does not allow multiple "looks" at the interventional data. Second, because two of the emphases of guideline implementation are the prevention and aggressive treatment of hypotension and hypoxia, including postimplementation cases might significantly bias the results.

Study Design and Selection of Participants

The EPIC database is made up of the subset of patients from the Arizona State Trauma Registry meeting EPIC study criteria for major traumatic brain injury (described below). The registry has detailed inhospital data on all trauma patients transported to the 8 state-designated Level I trauma centers in Arizona. The EPIC database contains both Arizona State Trauma Registry data and linked, detailed, out-of-hospital data. The necessary regulatory approvals for the EPIC project were obtained from the Arizona Department of Health Services and the state attorney general. The University of Arizona Institutional Review Board and the Arizona Department of Health Services Human Subjects Review Board approved the project; determined that, by virtue of being a public health initiative, neither the interventions nor their evaluation constitutes human subjects research; and approved the publication of deidentified data.

Patients aged 10 years or older with physical trauma who had a trauma center diagnosis consistent with traumatic brain injury (either isolated or multisystem trauma that included traumatic brain injury) and met at least 1 of the following definitions for moderate or severe traumatic brain injury were included: CDC Barell matrix type 1; *International Classification of Diseases, Ninth Revision* head region severity score greater than or equal to 3; and Abbreviated Injury Scale–head region score greater than or equal to 3.[41]

Excluded were patients younger than 10 years; those missing EMS systolic blood pressure, oxygen saturation, or other important confounders; those with lowest systolic blood pressure less than 40 or greater than 200 mm Hg; those with oxygen saturation less than or equal to 10%; and those who were transferred out of the reporting trauma center.

The age cutoff of less than 10 years was used primarily to simplify the analysis. For patients younger than 10 years, hypotension is defined as a systolic blood pressure less than 70 mm Hg+(age×2).[43,45] Given that this represents only 6.8% of the EPIC population, it would markedly increase the complexity of the analysis without substantially adding to the size of the study cohort. Younger than 10 years also makes sense as an age cutoff because we were not yet examining treatment (the purpose of the main study). The related cutoffs (such as $<$15 years and having ventilation rates=20 breaths/min versus $\geq$15 years and 10 breaths/min) are not relevant to this analysis.

Interventions

This was an evaluation of the preimplementation EPIC cohort and entailed no interventions.

Outcome Measures

The main outcome was survival to hospital discharge.[41]

Data Collection and Processing

The Arizona State Trauma Registry contains extensive trauma center data on all patients transported to the designated Level I trauma centers in the state. From the registry, all cases meeting study criteria (described above) are entered into the EPIC database. Each participating EMS agency then receives a list of the EPIC patients who were cared for in their system. The cases are matched by incident date, name, and other patient identifiers. Either scanned copies (paper-based patient care records) or electronic data files (electronic patient care records) are then sent to the EPIC study data center. Database personnel then use a comprehensive data collection tool to abstract the data and enter them into the EPIC database. This provides an extensive, linked data set for study patients that includes both out-of-hospital and trauma center data. The entire process of case identification, EMS and trauma center linkage, accessing EMS patient care records, trauma center and EMS data entry, data quality management, and the structure of the EPIC database are described in detail in the study methods article.[41] More than 20,000 cases have been enrolled in EPIC, and more than 31,000 EMS patient care records have been entered into the database. There are more patient care records than cases because many patients are cared for by more than 1 EMS agency. The successful linkage rate is exceptionally high (for example, throughout the study, the rate of cases with missing EMS systolic blood pressure has been consistently $<$5%).

Blood pressure and oxygen saturation data were evaluated by including every documented out-of-hospital measurement for each patient. This could include data from 1 or several EMS agencies for a given patient. Patients who had at least 1 systolic blood pressure measurement less than 90 mm Hg or oxygen saturation less than 90% within their entire set of out-of-hospital measurements became, respectively, the group with "hypotension" or "hypoxia." The "combined hypotension and hypoxia" cohort included all patients who had at least 1 hypoxic measurement and at least 1 hypotensive measurement during the entire duration of their out-of-hospital care.

Primary Data Analysis

Continuous variables were summarized by median and interquartile range within each of the 2 subgroups of patients who survived or died and also within each of the 4 groups defined by hypotension and hypoxia status (neither hypotension nor hypoxia, hypotension only, hypoxia only, and both hypotension and hypoxia). Categorical variables were summarized by frequency and proportion (with 95% confidence intervals [CIs] when appropriate) with each of the subgroups described above. Association between mortality and hypotension and hypoxia status was examined by logistic regression, with or without adjustment, for important independent risk factors and potential confounders (age, sex, race, ethnicity, payment source, trauma type [blunt versus penetrating], head region injury score [*International Classification of Diseases, Ninth Revision* matched to the Abbreviated Injury Scale], Injury Severity Score, interfacility transfer, and treating trauma center). Age, sex, race, ethnicity, head region injury score, Injury Severity Score, and interfacility transfer were included a priori in the model (regardless of whether they were found to be significant), whereas payment source, trauma type, and treating trauma center were included because they were found to be significant covariates. The effect of age in the logistic regression was fitted nonparametrically with penalized thin plate regression splines through the generalized additive model,[46] with the smoothing parameter chosen to optimize the Akaike information criterion. The software environment R (version 3.2.3; The R Foundation, Vienna, Austria) was used for the analysis[47] and the R package mgcv (version 1.8-12; Simon Wood, Bristol, UK)[46,48] was used for the generalized additive model. *P* values were calculated from a Wald-type test with the Bayesian covariance matrix.[49] The fitted model was assessed by deviance residual plots, as well as the area under the receiver operating characteristic curve. The 95% CIs of the area under the receiver operating characteristic curve were obtained by the Delong method.[50] Collinearity was checked with variance inflation factors for the parametric terms and concurvity for the nonparametric term. Mixed-effect models were used to assess the correlation of subjects treated by the same trauma center, and multiple imputation procedures were used to evaluate the effect of missing covariates.

Main Results

There were 17,105 subjects in the preintervention group (from January 1, 2007, through March 31, 2014), of whom 13,151 (76.9%) met inclusion criteria (study cohort; Figure 1 shows the details of excluded cases). The median age was 45 years (interquartile range 26 to 64 years), 68.6% were men, and 8.2% died. Among patients in the study group, 11,545 (87.8%) had neither hypotension nor hypoxia, 604 (4.6%) had hypotension only, 790 (6.0%) had hypoxia only, and 212 (1.6%) had both hypotension and hypoxia. Figure 2 shows the raw, unadjusted cohort mortality by the existence of neither hypotension nor hypoxia, hypotension only, hypoxia only, and both hypotension and hypoxia. The mortality rates ranged from a low of 5.6% for patients with neither hypoxia nor hypotension to a high of 43.9% for those with both. Table 1 summarizes the demographics and patient characteristics by survival status. Table 2 summarizes the same variables by hypotension and hypoxia status. All factors associated with risk of death were also associated with the hypotension and hypoxia status. The specific data by treating trauma center are not shown in Tables 1 or 2. Because absolute anonymity is required by state regulations and the institutional review board (for all subjects, EMS agencies, and hospitals), we were not able to report specific trauma-center-related data, even generically, because trauma center patient volumes in Arizona are a matter of public record. Thus, presentation of these data could lead to certain hospital-specific information's being inferred or identified (eg, because of comparisons of the sizes of the 95% CIs). Although the data are not shown, because treating trauma center was a significant confounder, we adjusted for it in the model.

Logistic regression was used to examine the independent associations between hypotension and hypoxia status and mortality risk, controlling for potential confounders and significant risk measures (Table 1). The results of the regression analysis are shown in Table 3. Figure 3 shows the crude (unadjusted) and adjusted ORs (cORs and aORs, respectively) for death for the subcohorts defined by hypotension and hypoxia status, using the patients with neither hypotension nor hypoxia as the reference. Compared with this group, the cohort with both hypotension and hypoxia had a cOR for death of 13.2 (95% CI 10.0 to 17.5) and an aOR of 6.1 (95% CI 4.2 to 8.9). These represent at least a doubling of the corresponding ORs for either hypotension (cOR 4.4 [95% CI 3.6 to 5.5]; aOR 2.5 [95% CI 1.9 to 3.3]) or hypoxia (cOR 6.6 [95% CI 5.6-7.9]; aOR 3.0 [95% CI 2.4-3.8]) alone (Figure 3). Testing for an interaction term between hypotension and hypoxia was not significant in the logistic regression model (P=.43), indicating that the effects of hypotension and hypoxia were additive on the scale of log odds.

Deviance residual plots did not indicate any deviation from the model assumptions. The only continuous

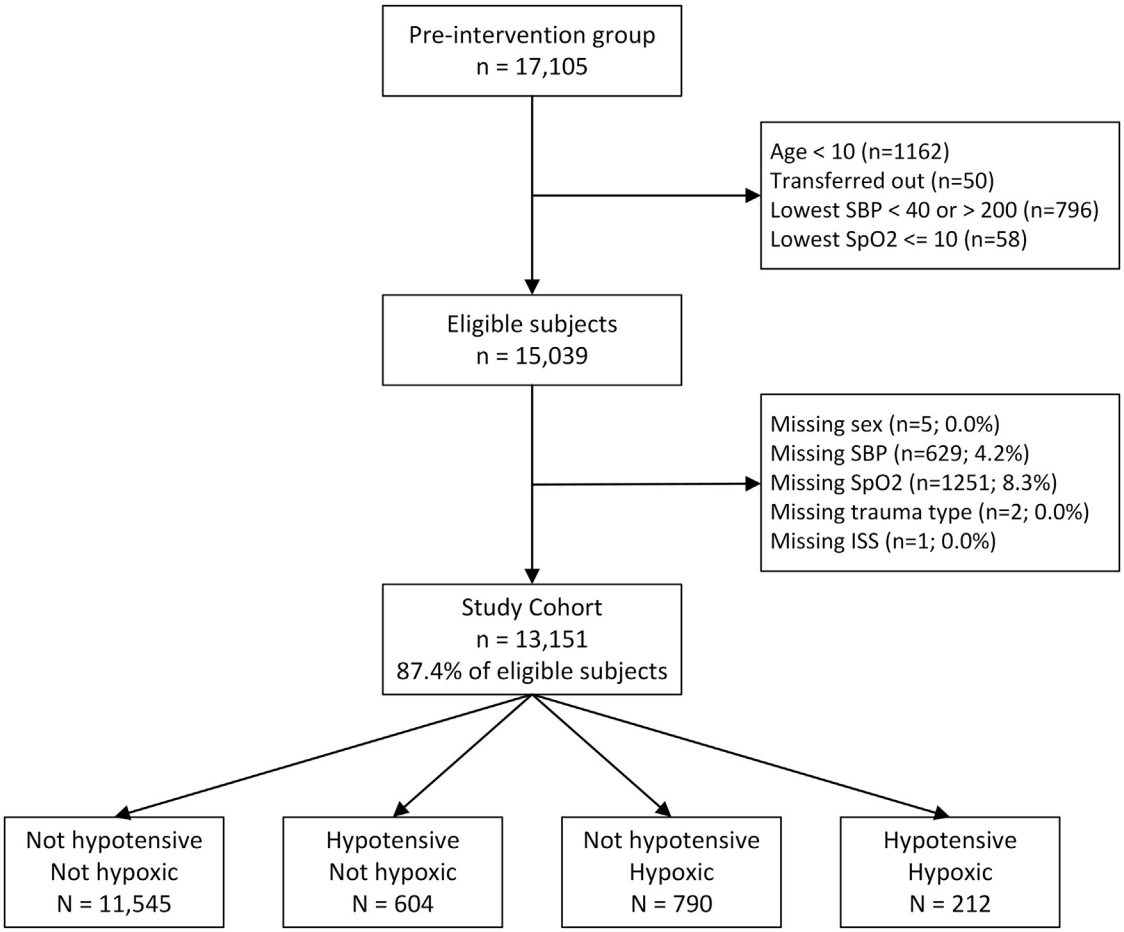

Figure 1. Details of study population inclusion and exclusion. *SBP*, Systolic blood pressure; *SpO2*, % oxygen saturation; *Trauma type*, Blunt or penetrating injury; *ISS*, Injury severity score.

covariate in the model, age, was fitted nonparametrically. The area under the receiver operating characteristic curve was estimated to be 0.938 (95% CI 0.932 to 0.945), indicating a high discriminative ability of the model. In addition, no multicollinearity in the covariates was detected.

As a sensitivity analysis, random trauma center effects were added to the logistic regression model to explore the potential correlation among subjects treated by the same trauma center. There was minimal difference in the results: the largest change in the estimated ORs was 1.5% for the 3 groups of hypotension only, hypoxia only, and both conditions compared with the referent group of no hypotension or hypoxia. Also, the largest change in the standard error estimates for the 3 corresponding regression coefficients was 0.2%. As another sensitivity analysis, we applied the multiple imputation procedure to explore the effects of missing data and observed only small changes. The largest change in the estimated ORs was 10.5%, and the lower limit of the 95% CI for each OR remained above 1.

LIMITATIONS

This study had limitations. First, the design was observational, and we were unable to establish cause-and-effect relationships related to treatment. Thus, the results cannot be used to determine whether the treatment of hypotension or hypoxia is effective at reducing mortality (this is part of the primary hypothesis of the main, parent study). The current analysis simply allowed us to identify associations between hypotension, hypoxia, and outcome.

Second, there are some missing data. However, for an out-of-hospital study, the rates for missing data were very low[51] (Figure 1). In addition, the use of multiple imputation resulted in minimal differences in the analysis compared with that of the actual data set.

Third, the database contains only those measurements of blood pressure and oxygen saturation that were documented by EMS personnel, and there is no way to independently verify the accuracy of the measurements. Thus, we could not know for certain that all hypotensive or hypoxic patients were identified, and hence there could be

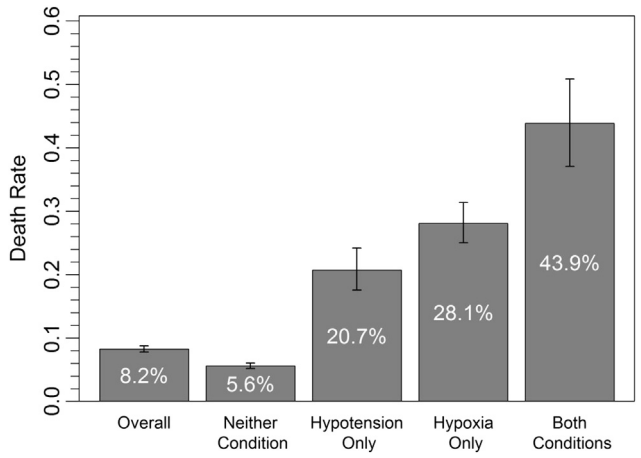

Figure 2. Crude mortality rate by hypotension and hypoxia status. Error bars represent 95% CIs.

some misclassification of patients among the 4 groups (hypotension, hypoxia, neither, and both). However, these issues related to data documentation and accuracy are true of essentially all EMS studies. One strength of EPIC is that the data are abstracted directly, consistently, and comprehensively from the patient care records. This level of scrutiny and consistency of data collection is rare in out-of-hospital research.[51]

Fourth, there could have been some "leakage" in practice changes during the preimplementation timeframe because the guidelines have been available for more than a decade. However, we believe it is unlikely that this is a factor. We conducted a prestudy evaluation of traumatic brain injury protocol changes and implementation before the EPIC project implementation to identify whether partial or full implementation was occurring in Arizona. Information from 51 agencies (responsible for EMS response to 4.8 million residents [75% of the population]) was gathered related to traumatic brain injury EMS care. Only half had protocols specifying appropriate ranges for oxygen saturation or blood pressure, and only one third had any specific treatment protocols. Even among agencies with traumatic brain injury protocols, the monitoring and treatment recommendations were highly variable, and no agency had implemented or was planning to implement the official traumatic brain injury guidelines.

Fifth, the definition for hypotension and hypoxia required only that there be at least a single low reading (<90 mm Hg/<90% saturation). Thus, the absence of time-sequence analysis means that we treated patients who may have had multiple low readings the same as those who had only a single abnormal measurement.

Sixth, we did not evaluate whether interventions were performed in an attempt to treat blood pressure or oxygenation.

Table 1. Patient and injury characteristics by survival status.*

Characteristics	All, 13,151	Alive, 12,067	Dead, 1,084
Age, y	45 (26–64)	44 (25–64)	50 (28–72)
Male patient			
No	4,135 (31.4)	3,808 (31.6)	327 (30.2)
Yes	9,016 (68.6)	8,259 (68.4)	757 (69.8)
Race			
Black	386 (2.9)	358 (3)	28 (2.6)
American Indian/ Alaska Native	1,087 (8.3)	1,007 (8.3)	80 (7.4)
Asian	129 (1)	118 (1)	11 (1)
White	9,868 (75)	9,047 (75)	821 (75.7)
Other	1,570 (11.9)	1,444 (12)	126 (11.6)
Unknown	111 (0.8)	93 (0.8)	18 (1.7)
Hispanic			
No	10,083 (76.7)	9,264 (76.8)	819 (75.6)
Yes	2,743 (20.9)	2,528 (20.9)	215 (19.8)
Unknown	325 (2.5)	275 (2.3)	50 (4.6)
Payer			
Private	4,292 (32.6)	4,037 (3,3.5)	255 (23.5)
AHCCCS/Medicaid	3,415 (26)	3,165 (26.2)	250 (23.1)
Medicare	2,846 (21.6)	2,544 (21.1)	302 (27.9)
Self-pay	1,698 (12.9)	1,515 (12.6)	183 (16.9)
Other	633 (4.8)	581 (4.8)	52 (4.8)
Unknown	267 (2)	225 (1.9)	42 (3.9)
Trauma type			
Blunt	12,665 (96.3)	11,782 (97.6)	883 (81.5)
Penetrating	486 (3.7)	285 (2.4)	201 (18.5)
Head ISS (*ICD-9*)			
1–3	7,182 (54.6)	7,104 (58.9)	78 (7.2)
4	3,874 (29.5)	3,747 (31.1)	127 (11.7)
5–6	1,962 (14.9)	1,099 (9.1)	863 (79.6)
Unknown	133 (1)	117 (1)	16 (1.5)
ISS (*ICD-9*)			
1–14	5,372 (40.8)	5,349 (44.3)	23 (2.1)
16–24	4,381 (33.3)	4,299 (35.6)	82 (7.6)
≥25	3,398 (25.8)	2,419 (20)	979 (90.3)
Hypotension			
No	12,335 (93.8)	11,469 (95)	866 (79.9)
Yes	816 (6.2)	598 (5)	218 (20.1)
Hypoxia			
No	12,149 (92.4)	11,380 (94.3)	769 (70.9)
Yes	1,002 (7.6)	687 (5.7)	315 (29.1)
Hypotension and hypoxia			
No	12,939 (98.4)	11,948 (99)	991 (91.4)
Yes	212 (1.6)	119 (1)	93 (8.6)
Interfacility transfer			
No	8,890 (67.6)	8,051 (66.7)	839 (77.4)
Yes	4,176 (31.8)	3,932 (32.6)	244 (22.5)
Unknown	85 (0.6)	84 (0.7)	1 (0.1)

AHCCCS, Arizona Health Care Cost Containment System; *ICD-9*, *International Classification of Diseases, Ninth Revision*.
*Data are presented as median (interquartile range) for continuous variables and No. (%) for categorical variables.

DISCUSSION

The detrimental effects of hypotension and hypoxia during the early care of patients with major traumatic brain injury have been well established.[6,7,10-40] However, there is almost nothing known about the effect of these factors

Table 2. Patient and injury characteristics by hypotension and hypoxia status.*

Characteristics	All, 13,151	No Hypotension or Hypoxia, 11,545	Hypotension Only, 604	Hypoxia Only, 790	Both Conditions, 212
Dead					
No	12,067 (91.8)	10,901 (94.4)	479 (79.3)	568 (71.9)	119 (56.1)
Yes	1,084 (8.2)	644 (5.6)	125 (20.7)	222 (28.1)	93 (43.9)
Age, y	45 (26–64)	45 (26–65)	44 (25–62)	48 (28.2–66)	32.5 (21–50)
Male patient					
No	4,135 (31.4)	3,633 (31.5)	202 (33.4)	236 (29.9)	64 (30.2)
Yes	9,016 (68.6)	7,912 (68.5)	402 (66.6)	554 (70.1)	148 (69.8)
Race					
Black	386 (2.9)	341 (3)	11 (1.8)	31 (3.9)	3 (1.4)
American Indian/Alaska Native	1,087 (8.3)	950 (8.2)	59 (9.8)	52 (6.6)	26 (12.3)
Asian	129 (1)	114 (1)	6 (1)	7 (0.9)	2 (0.9)
White	9,868 (75)	8,646 (74.9)	453 (75)	610 (77.2)	159 (75)
Other	1,570 (11.9)	1,405 (12.2)	69 (11.4)	78 (9.9)	18 (8.5)
Unknown	111 (0.8)	89 (0.8)	6 (1)	12 (1.5)	4 (1.9)
Hispanic					
No	10,083 (76.7)	8,837 (76.5)	456 (75.5)	625 (79.1)	165 (77.8)
Yes	2,743 (20.9)	2,430 (21)	124 (20.5)	145 (18.4)	44 (20.8)
Unknown	325 (2.5)	278 (2.4)	24 (4)	20 (2.5)	3 (1.4)
Payer					
Private	4,292 (32.6)	3,782 (32.8)	190 (31.5)	243 (30.8)	77 (36.3)
AHCCCS/Medicaid	3,415 (26)	2,958 (25.6)	180 (29.8)	208 (26.3)	69 (32.5)
Medicare	2,846 (21.6)	2,537 (22)	113 (18.7)	177 (22.4)	19 (9)
Self-pay	1,698 (12.9)	1,487 (12.9)	82 (13.6)	101 (12.8)	28 (13.2)
Other	633 (4.8)	552 (4.8)	22 (3.6)	44 (5.6)	15 (7.1)
Unknown	267 (2)	229 (2)	17 (2.8)	17 (2.2)	4 (1.9)
Trauma type					
Blunt	12,665 (96.3)	11,213 (97.1)	541 (89.6)	720 (91.1)	191 (90.1)
Penetrating	486 (3.7)	332 (2.9)	63 (10.4)	70 (8.9)	21 (9.9)
Head ISS (*ICD-9*)					
1–3	7,182 (54.6)	6,573 (56.9)	284 (47)	274 (34.7)	51 (24.1)
4	3,874 (29.5)	3,476 (30.1)	139 (23)	208 (26.3)	51 (24.1)
5–6	1,962 (14.9)	1,391 (12)	165 (27.3)	299 (37.8)	107 (50.5)
Unknown	133 (1)	105 (0.9)	16 (2.6)	9 (1.1)	3 (1.4)
ISS (*ICD-9*)					
1–14	5,372 (40.8)	5,090 (44.1)	137 (22.7)	132 (16.7)	13 (6.1)
16–24	4,381 (33.3)	3,986 (34.5)	168 (27.8)	198 (25.1)	29 (13.7)
≥25	3,398 (25.8)	2,469 (21.4)	299 (49.5)	460 (58.2)	170 (80.2)
Interfacility transfer					
No	8,890 (67.6)	7,662 (66.4)	410 (67.9)	641 (81.1)	177 (83.5)
Yes	4,176 (31.8)	3,808 (33)	191 (31.6)	144 (18.2)	33 (15.6)
Unknown	85 (0.6)	75 (0.6)	3 (0.5)	5 (0.6)	2 (0.9)

*Data are presented as median (interquartile range) for continuous variables and No. (%) for categorical variables.

when they both occur in patients before arrival at the hospital because the hypotension and hypoxia combination is an unusual occurrence, and studying this question requires the analysis of large numbers of patients with traumatic brain injury and linked out-of-hospital data. Although there are large trauma-center-based databases that can be queried for ED and inhospital information, these have limited or no out-of-hospital data.[22,38,39,52-57] Because the EPIC database has extensive out-of-hospital data and is very large, it provides the opportunity to ask EMS-related questions in small patient subgroups.[41]

We have been able to find only 2 previous studies that reported specifically on the combined effect of out-of-hospital hypotension and hypoxia on outcome.[6,16] In the investigation of 49 patients by Stocchetti et al,[6] 27 had an oxygen saturation less than 90% on the scene and 12 had a systolic blood pressure less than 100 mm Hg (their definition for hypotension). Unfortunately, the study does not report the number of patients who had both hypotension and hypoxia. However, at least some of the patients must have had both because the authors concluded that "outcome was significantly worse in cases of hypotension, desaturation, or both." They gave no information about the relative rates of mortality among the cohorts. Chi et al[16] studied 150 patients with severe traumatic brain injury who were transported by helicopter.

Table 3. Logistic regression model for death.

Covariates*	OR	95% CI
Hypotension and hypoxia status		
Neither hypotension nor Hypoxia	Reference	NA
Hypotension only	2.49	(1.87–3.32)
Hypoxia only	3.00	(2.37–3.78)
Both conditions	6.10	(4.20–8.86)
Male patient		
No	Reference	NA
Yes	0.98	(0.82–1.17)
Race		
Black	Reference	NA
American Indian/Alaska Native	1.82	(1.00–3.32)
Asian	1.31	(0.51–3.35)
White	1.72	(1.02–2.91)
Other	1.94	(1.06–3.56)
Unknown	2.23	(0.89–5.60)
Hispanic		
No	Reference	NA
Yes	0.73	(0.56–0.94)
Unknown	1.78	(1.08–2.93)
Payer		
Private	Reference	NA
AHCCCS/Medicaid	1.08	(0.85–1.37)
Medicare	1.29	(0.97–1.72)
Self-pay	2.49	(1.89–3.29)
Other	1.18	(0.79–1.76)
Unknown	2.75	(1.62–4.66)
Trauma type		
Blunt	Reference	NA
Penetrating	4.73	(3.55–6.31)
Head ISS (*ICD-9*)		
1–3	Reference	NA
4	1.34	(0.96–1.87)
5–6	12.35	(9.05–16.85)
Unknown	5.76	(2.97–11.16)
ISS (*ICD-9*)		
1–14	Reference	NA
16–24	3.08	(1.81–5.25)
≥25	12.93	(7.82–21.38)
Interfacility transfer		
No	Reference	NA
Yes	0.62	(0.50–0.77)
Unknown	0.25	(0.03–2.02)

NA, Not applicable
*Age was fitted nonparametrically and trauma center was also included (details not shown).

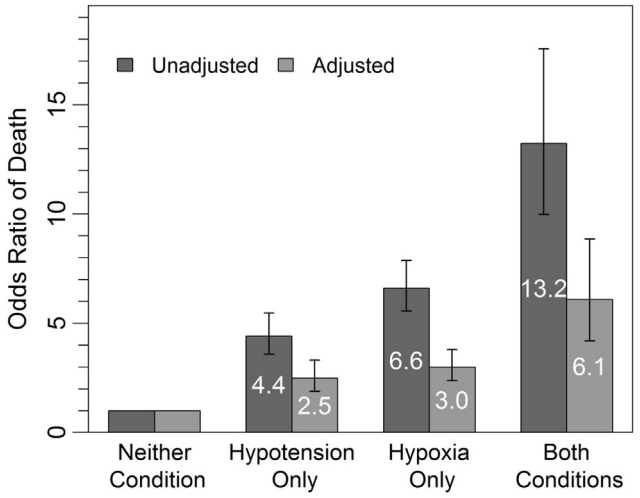

Figure 3. ORs for mortality by hypotension and hypoxia status. Reference group was the cohort with neither hypotension nor hypoxia. Error bars represent 95% CIs.

Fourteen patients had only hypotension, 37 had only hypoxia (oxygen saturation <92%), and 6 had both. Mortality for cases with neither hypotension nor hypoxia was 20% compared with 8% for hypotension-only patients, 37% for hypoxia-only patients, and 24% for those with both. These wide-ranging (and even paradoxic) results were likely due to the very small numbers, and thus this study could make no conclusions about the effect of the combination of hypotension and hypoxia on outcome. Both Fearnside et al[11] and Stassen and Welzel[40] also obtained out-of-hospital clinical data in their evaluations of severe traumatic brain injury. However, they made no comment about the relative influence of the combination of hypotension and hypoxia. In the classic study by Chesnut et al[10] on secondary brain injury, the authors attempted to assess the effect of physiologic insults in the EMS setting. Unfortunately, the out-of-hospital data were compromised by the fact that they did not actually obtain measurements of oxygenation. Rather, out-of-hospital "hypoxia" was merely identified as the presence of cyanosis or apnea when this was documented by EMS personnel.[10]

The studies that report inhospital data from the ED or the ICU give slightly more information about the combination of hypotension and hypoxia, but the findings have been variable and inconclusive. Manley et al[26] studied 107 patients with traumatic brain injury, using physiologic measurements in the ED and inpatient settings. Among the 14 patients who had both hypotension and hypoxia, they found that "…the combination of hypotension and hypoxia…[was] not additive." Unfortunately, with such small numbers, the statistical power behind such a conclusion was limited. Pigula et al[22] evaluated 451 children with severe traumatic brain injury in the National Pediatric Trauma Registry, using inhospital physiologic parameters. Mortality was 61% among children with hypotension only, 21% among those with hypoxia only, and 85% among the small number (20) who had both hypotension and hypoxia. They concluded that "[i]f both hypotension and hypoxia were found together, mortality was only slightly increased over those children with hypotension alone (p=0.056)." Kohi et al[35] found that the combination of hypotension and hypoxia in patients with severe traumatic brain injury was universally fatal.

However, there were only 6 patients in this cohort and all of the measurements of blood pressure and oxygenation were obtained in the ICU. Thus, this study was reflective of patients with "late" hypotension and hypoxia, but provided no information about physiologic insults occurring earlier in the course and, perhaps, before irreversible injury had occurred. In a meta-analysis, McHugh et al[39] reported on 465 patients with combined hypotension and hypoxia and found a slight increase in mortality among those who had both (54.6%) compared with those with hypotension only (48.5%). However, they used a mixture of ED admission data and an unspecified amount of EMS data. There was also significant heterogeneity among the investigations that were included in the final meta-analysis (eg, differing definitions of hypotension). Furthermore, some of the studies had missing data rates exceeding 30%, creating substantial risks for selection bias.

In the current study of 13,151 patients with major traumatic brain injury, 604 (4.6%) experienced hypotension without hypoxia in the field, 790 (6.0%) had hypoxia without hypotension, and 212 (1.6%) experienced both. We believe this is the largest evaluation of out-of-hospital hypotension and hypoxia yet conducted in patients with traumatic brain injury, and this allowed us to examine detailed interactions that the previous studies could not (the largest report in the extant EMS literature had no more than 12 patients with combined hypotension/hypoxia[6,16]). In the EPIC population, the combination of hypotension and hypoxia is associated with a significantly increased likelihood of dying (cOR 13.2; aOR 6.1) compared with the cohorts who have only hypotension (cOR 4.4; aOR 2.5) or hypoxia (cOR 6.6; aOR 3.0) (Figure 3). This means that the combination is associated with more than a doubling of the risk of death compared with having either alone. The clinical implications of this are further supported by the fact that there is no interaction on the log odds scale. In other words, hypoxia does not modify the effect of hypotension and, conversely, hypotension does not modify the effect of hypoxia. Thus, in patients who experience both hypotension and hypoxia, the combination of these physiologic insults has a profound influence on outcome, with an additive influence on the log odds of death.

As stated in the study hypothesis, the primary focus of this evaluation was to identify whether the hypotension and hypoxia combination adds additional risk above that of either alone. However, this analysis also revealed another important finding: the associations between the secondary physiologic insults and mortality are significantly stronger than have been generally reported. Although there is variation, both the crude and adjusted odds of death for patients experiencing hypoxia alone have typically been approximately 2.[7,10-13,17,20] However, in the EPIC population, the cOR is 6.6 and the aOR is 3.0 (Figure 3). Furthermore, the odds of mortality in patients with hypotension only have generally been in the range of 1.3 to 2.[10,11,14,15,18-38] In contrast, we identified significantly higher odds of death in hypotensive patients (cOR 4.4; aOR 2.5) (Figure 3). There are several potential reasons for this. First, perhaps the previous studies were simply too small to identify an accurate influence of these factors. Second, many of the studies that depended on obtaining data from trauma center databases had access to only 1 or 2 out-of-hospital vital signs measurements. Thus, it is unclear whether hypotension or hypoxia was reliably identified because in previous studies it was unclear whether the EMS measurements recorded in the database were the first, last, highest, or lowest for each patient. By comparison, in the EPIC database, there is no limit to the number of vital signs measurements that can be recorded. For example, there are cases in the EPIC database that have more than 30 recorded out-of-hospital blood pressure measurements. Finally, most of the previous studies used blood pressure and oxygen saturation data obtained after arrival at the hospital. Thus, it is possible that the EPIC study, by specifically evaluating the out-of-hospital treatment interval, has identified patients who become hypotensive or hypoxic earlier in their course. In this case, the effects of these insults may be magnified by occurring earlier and perhaps lasting longer, and thus may affect the brain to a greater extent.

The design of the current study does not allow confident statements about the effect of EMS treatment aimed at preventing or reversing hypotension or hypoxia. However, it does bring up some interesting questions. Because the combination appears to be so detrimental, this raises the specter that if either hypoxia or hypotension can be prevented or treated, there may be the potential to significantly improve survival even if the other parameter is not improved. For example, the prevention of hypoxia by management of oxygenation may decrease a given patient's risk of death from a highly fatal aOR of 6.1 (if he or she experienced both hypotension and hypoxia) to a far more "favorable" aOR of 2.5 (if he or she experienced only hypotension). The same might be relevant in the prevention or treatment of hypotension in a patient who has hypoxia that cannot be improved.

In summary, this statewide study evaluating out-of-hospital hypotension and hypoxia in victims of major traumatic brain injury found a greater risk for death from either of these insults than has generally been reported in the previous literature. Furthermore, the combination of hypotension and hypoxia occurring before arrival at the

hospital is associated with a significant increase in both the crude and adjusted odds of death compared with either physiologic insult alone. In fact, the effects are additive on the log odds of death. These findings seem supportive of the emphasis on aggressive prevention and treatment of hypotension and hypoxia reflected in the current EMS traumatic brain injury treatment guidelines but clearly reveal the need for further study to determine their influence on outcome.[42-45]

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